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## ORIGINAL ARTICLES.

### TOXIC CIRRHOSIS RESULTING FROM ACUTE LIVER ATROPHY.

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Whether recovery ever occurs in acute liver atrophy has long been a mooted question. Frerichs,[1] who gave the first accurate clinical description of the disease was very doubtful whether recovery ever took place. Osler,[2] in the first edition of his text book (1892) as well as in all subsequent editions asserted that he had seen a case that was convalescent in Leube's clinic in Wurzburg. von Leube,[3] himself, stated years later that he had had only 2 cases that recovered. In both there had been an undoubted shrinkage of the liver and in one leucin and tyrosin were found in urine over a period of weeks. It was doubtless one of these two cases that Osler saw. In spite of having had recoveries in what he regarded as undoubted acute atrophy, von Leube emphasized the rarity of such an outcome. If health is regained, he says, after the diagnosis of acute yellow atrophy has been made it is more than probable that the diagnosis was false. Albu[4] in 1901, reported what seemed to be an undoubted case of acute yellow atrophy, and there were others. F. W. White[5] found that up to 1908 there were between 20 and 30 cases of recovery reported in the literature. The evidence, however, was not absolutely convincing and Pel,[6] the distinguished Amsterdam clinician, as late as 1909 said that among liver diseases acute yellow atrophy occupied the same position as acute miliary tuberculosis among

the diseases of the lung. *La mort sans phrase* was the prognostic designation he applied to it.

To prove the possibility of recovery more evidence was needed than can be obtained from clinical study alone. Pathologic anatomy gave additional evidence of the possibility of recovery. Regeneration of liver tissue in cases dying late in the disease was repeatedly observed. Sometimes the regeneration was extensive. Marchand,[7] in 1895, studied a remarkable instance of regeneration. Catarrhal jaundice had developed six months before death. The jaundice disappeared, but recurred and persisted. The onset of serious symptoms did not take place until a few days before death. The liver weighed 1240 gm. and contained many nodules composed of hyperplastic liver cells. Marchand recognized that the nodular hyperplasia was the result of a previous acute yellow atrophy. Since then a good many similar cases have been described and earlier ones collected from the literature. One of the best papers on the pathologic anatomy of this condition is that of M'Donald and Milne.[8]

Definite proof of recovery from acute liver atrophy was first furnished by Umber.[9] A jaundiced patient, a girl aged eighteen years, in his clinic, presented typical symptoms of acute liver atrophy. During convalescence on the forty-first day after the onset she was seized with severe colicky pains with vomiting and increased icterus. A diagnosis of cholecystitis was made. Two weeks later an operation was performed. The liver was small, fairly smooth and of bright red color. The border, especially of the right lobe, and a portion of the liver near the ligamentum falciformis was shrunken. A bit of tissue was excised and showed on microscopic examination healing acute atrophy. The girl was well three years later. Similar cases of acute or subacute liver atrophy have since been reported by Huber and Kausch,[11] Strauss,[12] Braun,[13] Brütt,[14] and Römer.[15]

Mallory[16] in 1911 published his studies on cirrhosis of the liver, which threw light on a dark domain in pathology. He showed that the anatomical classification of the cirrhoses could be based on changes in the liver cells and the connective tissues brought about by disease. Excepting old healed cirrhosis he was able to divide all the cases of cirrhosis of the liver into five types, each with its characteristic primary cell lesion. He gave no clinical data of his cases and confined himself to the gross and microscopic pathology.

Can acute liver atrophy terminate in cirrhosis? This question has been often asked in recent years. Mallory[16] not only asserted that it did, but he maintained that it produces a special type of cirrhosis which can be distinguished from the other forms of cirrhosis on histologic examination. To this type he has given the name toxic cirrhosis. "It ought to be possible," he wrote in 1911, "to recognize the resulting type of cirrhosis long after the acute lesion is over even without a clinical history to help." The liver in this

condition according to his description may present great irregularity of outline, only exceeded by the syphilitic liver. Sometimes it may resemble closely the liver of alcoholic cirrhosis, but the nodules usually vary more in size. Excessive regeneration of liver cells often results in the formation of nodules; the hyperplastic nodules frequently found in old cases of acute liver atrophy. In these nodules, Mallory[17] points out, there is no lobular arrangement and no bile ducts. He first recognized that the destructive lesion, extensive necrosis of the liver cells, is always an acute process, never a slow progressive one. The necrosis begins in the centers of the lobules and spreads peripherally. If it involves only the central portion of the lobule, removal of the necrotic cells and regeneration may be completed within ten days. If all the cells in a lobule are killed, no regeneration of liver cells in that lobule takes place. The bile duct epithelium proliferates to a slight extent but does not form liver cells. New formed bile ducts may be seen in the outer zone of the lobules, but they never extend into the central half. "In the atrophied portions where there are no liver cells left the original lobular arrangement, much shrunken, can almost always be made out even if these parts have been stretched and pulled out of shape by excessive regeneration of liver cells in other parts. It is the only type of cirrhosis in which the condition occurs." (Mallory.[17])

Mallory's earlier work, published in 1911, has not attracted the attention it deserved from either pathologists or clinicians. Osler and McCrae[18] in their text-book, stated that clinically this type, that is the toxic cirrhosis, "can scarcely be spoken of as cirrhosis." This is true only of the earlier stages of the process which are more properly termed subacute liver atrophy, and the subchronic stage with multiple nodular hyperplasia (Seyfarth[19]).

That the late stage of the same process is a real cirrhosis clinically as well as pathologically is clearly shown by our first case. To the healed stage, Mallory's term toxic cirrhosis is preferable to chronic form of liver atrophy proposed by Seyfarth.[19] Its similarity to cirrhosis was recognized by Seyfarth in his study of material in Marchand's Institute. "We have seen presented at autopsy," he says, "nine months to years after the original disease a picture that could not be distinguished from a coarsely nodular cirrhosis." Mallory's chief contribution to the subject, it should be repeated, is in showing that such a cirrhosis can be distinguished histologically from other types of cirrhosis.

Our first case presented at postmortem examination a hobnailed liver. It was regarded as an ordinary portal cirrhosis of the alcoholic type by two able pathologists that examined it histologically. Sections were given to Mallory and without knowing anything of the clinical history he unhesitatingly diagnosed it as a toxic cirrhosis of the healed stage of an acute liver atrophy.

**Case Reports.** CASE I.—*Toxic cirrhosis, late stage. Three attacks of jaundice. Death (during mild attack of subacute atrophy) from perforating peptic ulcer of duodenum.* P. T., aged sixty-five years, was a merchant and a man of good habits who took little, if any, alcohol. There was no history of syphilis. Early in 1922, after he had had discomfort in the epigastric region for about ten

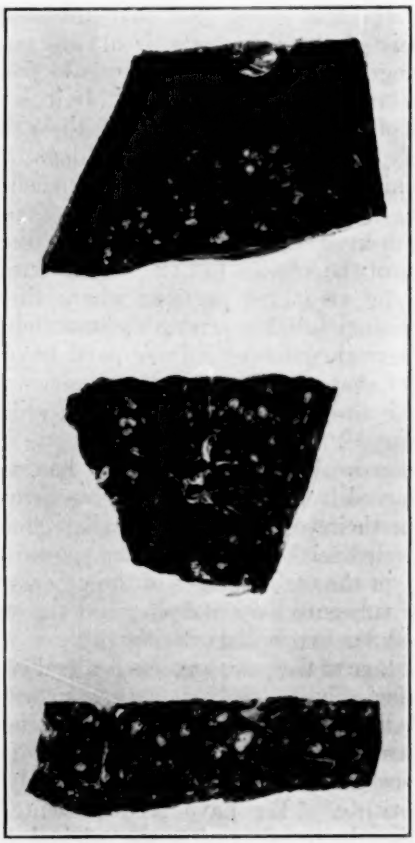

FIG. 1.—Toxic cirrhosis, advanced stage. CASE I. Appearance of the liver on section. On fresh examination the nodules that are white in the photograph were of greenish color. They were separated by bands of reddish color. The surface of the liver was coarsely nodular.

days, icterus developed. The jaundice became marked. The stools were acholic. There was no actual pain, and nothing then or previously suggestive of biliary colic. He had no fever. During this attack the liver was at times palpable. He recovered completely in a few months. In July, 1924, he had a second attack of jaundice which lasted only a few weeks. He lost during this illness

considerable weight and strength which he did not fully regain. A third attack of jaundice occurred early in June, 1925. It developed slowly, but reached a high degree and was present at the time

FIG. 2.—Toxic cirrhosis. Section of the liver in CASE I. The liver cells have entirely disappeared from many lobules, only connective tissue and bile ducts remaining. In the center of these shrunken lobules the stroma is condensed; in their peripheral portion are the proliferated bile ducts. One lobule is shown in which the parenchymal liver cells are fairly well preserved.

of his death on July 24, 1925. He never had ascites. The stools contained bile and much bile was obtained by biliary drainage (Lyon's method). Death was due to the perforation of a symptomless duodenal ulcer.

*Autopsy.* On opening the peritoneal sac the presenting loops of intestine are injected, moderately distended, serosa smooth. About four liters of clear bile stained fluid was removed. Many shreds of fibrin are found in the posterior portion of the abdominal cavity and in the pelvis. The liver extends to the costal border. It is small, firm and hard, its weight estimated to be about 1000 gm. The surface is greenish brown and everywhere coarsely nodular—a typical cirrhosis of Laennec. On section, resistance is much increased, the surface mottled, showing greenish nodules separated by bands of reddish color. The gall bladder is distended with about 300 cc. of apparently normal bile. Its wall is flexible, but edematous. It is about 5 mm. thick. The common duct is not dilated, the mucosa bile stained. The spleen is not enlarged, deep red, and very little pulp scrapes away with the knife.

*Microscopic Examination of the Liver.* Islands of parenchyma up to 2 and 3 mm. in size are surrounded by broad bands of connective tissue. The striking feature is the presence of large areas in which no liver cells are present; in these only shrunken lobules are seen with condensed stroma in the centers and proliferated bile ducts at the peripheries. Many of the liver cells are large and many bile capillaries are filled with bile. There is no necrosis of liver cells, but endothelial cells contain inclusions, evidently the remains of liver cells that had undergone necrosis during the recent attack.

*Comment.* Here is a case of marked cirrhosis resembling closely the ordinary hobnailed liver of Laennec. The man had had three attacks of jaundice without pain or fever. The diagnosis of catarrhal jaundice was supported by recovery from the illness. There was no ascites. The liver in the first attack was enlarged, but not in the two subsequent attacks. It was in reality a case of recurrent mild acute or subacute liver atrophy with recovery from the first two attacks and it is quite possible the third attack would have terminated in recovery if death from an intercurrent disease had not taken place. There were no signs of obstruction to the portal circulation except that the amount of fluid in the peritoneum was more than is usual in general serofibrinous peritonitis and might have been present before the perforation occurred.

CASE II.—*Toxic cirrhosis. Mild jaundice. Piece of liver removed at laparotomy. Recurrent ascites. Death. Duration fifteen months.* E. A., a woman aged fifty years, first consulted Dr. A. P. Lowell of Fitchburg, for epigastric distress in May, 1924. In August, 1924, distress in the epigastrium and under the right scapula became so severe that she took to her bed for a while. The symptoms dis-

appeared, but recurred late in December, 1924, when she became jaundiced and bile was found in the urine for the first time. The epigastric pain continued, but was never severe and never sudden. There was no fever. The stools contained bile. A gall stone in the common duct was suspected and on April 18, 1925, a laparotomy was performed by Dr. John T. Bottomley. The liver was hard and nodular, bluish gray in color. The gall bladder was distended with bile. The common duct was normal. Soon afterward the abdomen filled with fluid. The ascites recurred and she was tapped about thirty times. She became more and more emaciated and died in March, 1926. No autopsy was performed.

*Microscopic Examination of Excised Bit of Liver.* (Dr. Mallory.) Toxic cirrhosis. Over relatively large areas the liver cells have entirely disappeared, only bile ducts and cellular connective tissue remaining. In other areas liver lobules are intact. There is considerable infiltration of perilobular tissue with lymphocytes. No polymorphonuclear leukocytes are present. There are some nodules of liver cells 3 to 5 mm. in size composed of parenchymal cells without lobular arrangement. These are the hyperplastic nodules described by Marchand and later writers.

*Comment.* This is a case of shorter duration than Case I, but with a clinical picture of portal cirrhosis. Ascites is the most prominent symptom here, while jaundice was the chief clinical manifestation in the former case. The histologic picture of cirrhosis presented by the liver in the two cases was similar.

Through the courtesy of Dr. F. B. Mallory we have been able to analyze the cases of toxic cirrhosis that have been studied in the pathologic laboratory of the Boston City Hospital. The pathologic records since early in 1897 have been examined. Among 5417 autopsies there were only 7 cases of toxic cirrhosis, but the number in the records was increased by extramural autopsies and surgical specimens to 14. In addition there were 20 old healed cases of cirrhosis in which the type was not clearly determined, possibly in most instances toxic cirrhosis, but more probably, in part at least, due to cardiac disease—the so-called cardiac cirrhosis.

The cases typical, from a pathologic point of view, of toxic cirrhosis were 14 in number. The livers were all small, and firm, and coarsely nodular. They varied in weight from 670 to 1630 gm. The nodules were usually of greenish color and composed of bile stained liver cells separated by reddish firm bands that were made up of vascularized connective tissue. In several instances the spleen was notably enlarged. In one case occurring in a girl, aged seventeen years, the spleen weighed 620 gm., which was only 50 gm. less than the liver. This was an old toxic cirrhosis. The largest spleen weighed after preservation 780 gm. The liver from the same case was very coarsely nodular. A photograph of the liver appears in Mallory's recent paper[17] (Fig. 16).

In 2 of the cases of toxic cirrhosis in a late stage there was no history of either jaundice or ascites.

CASE III.—*Toxic cirrhosis with multiple nodular hyperplasia. No symptoms of acute liver atrophy. Death due to ruptured esophageal varix.* Esther G., aged fourteen years, gave a negative past history. There had been no gastrointestinal disorder. She came home from school one day complaining of nausea. An enema resulted in a black stool followed by several other movements of the same type. During the night she vomited fresh blood and clots about six different times. On admission to the Boston City Hospital, the physical examination revealed nothing of importance except a marked anemia. She died soon after her entrance to the hospital. Autopsy showed that the fatal hemorrhages had been due to the rupture of a dilated esophageal vein. The spleen weighed 695 gm.; firm consistence; surface smooth. On section it was smooth, brownish, with prominent connective tissue elements; small amount of pulp. The liver weighed 1630 gm. The surface was irregular due to the projection of several rounded masses varying in size from a pea to a walnut. "These are most numerous on the under surface and one such mass near the caudate lobe protrudes so markedly that it gives the appearance of an extra lobe. The capsule is thick and pale and the color of the organ on the surface is a light brown. In places, particularly on the upper surface, dilated veins may be seen. Section through one of these nodules shows pale, light brown translucent liver tissue, apparently young. Section through the liver as a whole reveals many of these areas of regeneration scattered throughout. The intervening portion consists of lighter colored areas, the surface of which is somewhat more opaque and shows streaks of fibrous tissues. On the cut surface, the rounded nodules stand out about 2 mm. above the surface of the background. The gall bladder wall is about 1 cm. in thickness, the increase being due to an excess of fluid in the tissues, giving it a jelly-like consistence."

*Microscopic Examination.* Toxic cirrhosis. The liver cells occur in rounded areas varying in size from a few cells to masses 5 mm. in diameter. Between these areas there is a dense connective tissue structure. The majority of liver cells are arranged in clumps and are not grouped about a central vein. The binding structure is for the most part coarse and dense. It contains many pinched off bile ducts. In it there is an inflammatory reaction of various grades of chronicity. In places the reaction is absent, in others it shows as scattered lymphocytes or foci of these cells, in still others there are endothelial leukocytes and eosinophiles, and in several places, particularly near the liver parenchyma and often within the liver cell masses, collections of polymorphonuclear leukocytes, always grouped about bile ducts.

*Comment.* In this case the liver atrophy had been so mild that it did not produce illness, yet the resulting cirrhosis led to the formation of esophageal varices and was associated with great enlargement of the spleen. Absence of symptoms of liver insufficiency was probably due to the large amount of uninjured liver tissue. The liver at death was the largest in our series.

CASE IV.—*Toxic cirrhosis. Edema of legs and eyelids at times. Bile in urine, palpable spleen. Death from acute mastoiditis.* Ethel S., aged seventeen years, was under observation in Dr. M. Ladd's clinic at the Boston Dispensary for nearly two years prior to her death. In the summer of 1924 she developed edema of the ankles and her weight increased 18 pounds. The urine was free from albumin and sugar. In September, the eyelids became edematous, but the swelling here quickly disappeared. On September 10 it was noted that there was moderate pitting of the ankles and legs to the knees. The scleræ were slightly yellow on November 7, but not on November 12. Bile was discovered in the urine on November 10, but on November 13 it was absent. A blood examination by Dr. R. Larrabee in January, 1925 showed a slight anemia: hemoglobin 74 per cent (Sahli); erythrocytes 4,800,000; leukocytes 9100, of which 80 per cent were polynuclears. In February, bile was again present in the urine at several examinations. The spleen was just palpable. Jaundice did not develop, and there was no ascites. She died in March, 1925, of septicemia following an acute mastoiditis.

*Autopsy.* The liver weighed 670 gm., was very small, the surface roughened by nodules about the size of marbles, pale yellowish brown and quite firm. It was very resistant to cutting. The spleen weighed 620 gm., was very firm, purple.

*Microscopic Examination.* Well marked cirrhosis with fairly broad bands of connective tissue containing groups of liver cells.

*Comment.* Acute liver atrophy so mild in its clinical manifestations that definite jaundice never developed and the only evidence during life, of liver disease was the occasional presence of bile in the urine.

CASE V.—*Toxic cirrhosis. Splenomegaly. Chronic ulcerative colitis.* Richard J., aged fourteen years, had diarrhea and weakness for four years. There was no jaundice or ascites. The liver weighed 1200 gm. and was coarsely nodular. Dr. Mallory who made the autopsy wrote the following comment at the end of the protocol. "This liver represents the late healed stage of an acute toxic (acute yellow atrophy) type of cirrhosis. Cause of primary lesion is not apparent. The spleen hypertrophy is due to chronic dilatation as the result of obstruction to the portal circulation caused by the cirrhotic liver."

In still another case of toxic cirrhosis in a young person there was no history of any acute illness during the time when the acute atrophy must have occurred and the patient had never been jaundiced. She was a girl aged fifteen years and was considered perfectly well. One morning on dressing to attend school she discovered that her abdomen had become so swollen during the night that she could not put on her corsets. When admitted to the Boston City Hospital eleven days later, the abdomen was greatly distended with fluid. She died a few days later of a pneumococcus septicemia. The liver weighed 905 gm. It was very firm and coarsely nodular. A photograph of this liver (Fig. 15) will be found in Mallory's recent paper.[17] The spleen weighed 645 gm. Microscopic examination of the liver revealed a toxic cirrhosis in the healed stage. Until the histologic study was made it was thought to be an alcoholic cirrhosis.

**Conclusions.** Classical acute yellow atrophy of the liver as described pathologically by Rokitansky and clinically by Frerichs, is simply a severe, rapidly fatal type of a disease that also occurs in a mild form, which may produce no symptoms during the acute stage, but ends in cirrhosis. This cirrhosis is of a special type somewhat resembling alcoholic cirrhosis and often mistaken for it. The histologic characteristics of this type of cirrhosis have been described by Mallory. To it he has given the name toxic cirrhosis. The late or healed stage, as shown by the cases reported in this paper are an actual cirrhosis in a clinical as well as a pathologic sense. Clinically the picture is varied. Even jaundice and ascites may be absent. The evidence presented in this paper justifies the conclusion that the work of Mallory has furnished the connecting link between acute liver atrophy and a definite type of cirrhosis.

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## DOES HYPERPLASIA OFFER ANY EVIDENCE FOR THE THYROGENESIS OF GRAVES' DISEASE?

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When a mental concept is adorned by a word, there is a disposition to accept the word as a verification of the concept. The idea was formed that the thyroid gland was blamable for superfunction that produced a chain of symptoms known as Graves' disease. The word "hyperthyroidism" promptly sprang into common use and seems generally to have suppressed any criticism of the truth of the concept that gave origin to the word. Hypothyroidism had been abundantly proved by therapeutic and experimental studies and apparently prepared the way for an easy acceptance of its antithesis "hyperthyroidism." The word has been so abundantly used that physicians generally have not stopped to inquire if the concept behind the word has been proved.

Thousands of patients suffering from Graves' disease have been subjected to resection of a large portion of their thyroid glands because the gland was enlarged from what is known as hyperplasia, a process that is characterized by enlargement of the thyroid cells and an increase in their number and by increased arterialization of the gland. This seems to plead strongly for superfunction of the thyroid and the logic of it all demands that the patient should be freed from a sufficiently large part of the gland so that the amount of the internal thyroid secretion will be reduced to a normal amount. This is the frank statement made by earnest advocates for amputative therapy. Under the pressure of criticism, however, they have

recently modified their position by saying that whether or not we are dealing with hyperthyroidism, amputation of a large part of the thyroid gland breaks the "chain" that is responsible for the disease. Where the chain begins or where it ends and of what the "chain" may consist is not mentioned. They also plead that they, that is, the operators and the patients, are satisfied with the results, so why should there be any question about the efficacy of the procedure.

The same argument in its time has supported the prestige of the "King's Touch," Exorcism of Evil Spirits, "Perkinism," osteopathy and chiropractic. So there has been in ancient and modern therapy little profit derived from this kind of reasoning in the search for truth.

**Hyperplasia and Enlarged Arterialization.** Hyperplasia and increased arterialization in moderate and extreme disease are found alike in cretinism, myxedema and in Graves' disease, and also in persons who present no evidences for any disease associated with altered thyroid function. Histologically, the gland of a cretin pup cannot be differentiated from the hyperplastic gland of Graves' disease and myxedematous patients often have large goiters with greatly enlarged thyroid arteries. The hyperplastic gland of the cretin pup reverts to the colloid state under the administration of iodin and so will the gland of Graves' disease, and also that of myxedema. I have seen goiters of myxedema that were unmodified by iodin when given in small amounts and also in doses of 15 gr., three times daily, that promptly disappeared with cure of the patient when exsiccated thyroid was given in doses of $1\frac{1}{4}$ gr., three times daily.

The explanation offered is, that when hyperplasia becomes so severe as to border on necrosis of the cells, the gland is no longer capable of elaborating the normal thyroglobulin from ingested iodin and therefore the ready-made biologic product must be employed to procure results.

I have treated only one case of early Graves' disease in which the hyperplasia was not affected by iodin and did subside under the administration of thyroidin. It may be that this patient's gland would have reverted to the colloid state had iodin been given in larger doses.

When a thyroid once enlarged by hyperplasia reverts to the colloid state, it has returned to as nearly the normal state as is possible. What do we find histologically in Graves' disease when reversion from hyperplasia to the colloid state has occurred before operation? The gland is as near the normal as it can ever be—in fact so far as we know it is functionally, a normal gland. What effect does resection of a large part of a normal thyroid have on the histology of the remaining portion? Hyperplasia is the result—the very histologic finding that inspires amputation of half or more of a hyperplastic or colloid gland for the cure of Graves' disease. What

happens in Graves' disease when the thyroid is resected? The remaining portion becomes hyperplastic and as a result operators have been known to pare off three succeeding eminences in a single thyroid after operation for Graves' disease. In other words the original resection begot three succeeding operations to combat hyperplasia in the remainder of the gland, the very thing for which the first operation was done.

No surgeon would knowingly amputate half the goiter of a patient suffering from myxedema and yet the same histologic process that suggests operation for Graves' disease is found in myxedema. For that matter the association between goiter and cretinism was the first observation that led to the belief that function of the thyroid gland has any importance in mental and physical development. What is still further striking in comparing the significance of hyperplasia in myxedema and Graves' disease is the fact that exactly the same hyperplastic process that occurs in the two diseases is amenable to the same kind of treatment, but when a reversion to the colloid state is obtained in myxedema the symptoms of the disease disappears, but in Graves' disease the symptoms may persist or after a temporary remission the symptoms may all recur without a return of the hyperplasia.

The goiters removed in Graves' disease present every degree of hyperplasia and also the colloid state which is as near the originally normal gland as can ever be attained.

This is an important point, because the advocates for hyperthyroidism or dysthyroidism have pleaded that although the hyperplastic gland is poor in iodin containing colloid, there may be an excess of the internal secretion delivered to the blood or some noxious modification of the normal internal secretion may be produced and thus give rise to the group of symptoms. The fact that there may be reversion from hyperplasia to the colloid state without abolishing the symptoms must be accepted as a strong argument against the histology of the gland offering any evidence for the thyrogenesis of the disease.

There is another clinical experience which offers some strong evidence against Graves' disease being dependent on hyperplasia of the thyroid gland, and that is the disappearance of goiter coincidentally in the development of the disease or with a severe exacerbation of all the symptoms. I have seen two such cases—both proved fatal and they were two of the very few fatalities I have seen in unoperated cases. In one of these cases, a girl aged eighteen years, the goiter was much reduced in size and in the other, a man aged sixty years, in whom the goiter was as large as a goose's egg, not only did the goiter disappear as severe symptoms began, but the protrusions from the enlarged right and left lobes and isthmus were replaced by depressions so that no evidence remained for a thyroid of normal size. In the latter case there was excellent evi-

dence for severe hypothyroidism so far as the diminished size of the gland, and the want of enlarged thyroid arteries were concerned.

These experiences justify the statement that in cretinism, myxedema and Graves' disease we may have either enlargement or diminution in size of the thyroid gland, and also that so far as any facts are available the histologic changes in all three conditions are identical and in all of them the hyperplasia responds in the same manner to treatment with iodin and with exsiccated thyroid. That myxedema is attended with hypothryoidism is abundantly proved. How can we be reconciled to acceptance of the same histologic evidence as proof for hyperthyroidism in Graves' disease? Certainly the weight of the logic of facts rests lightly on a mind that is convinced by such evidence.

It is true that hyperplasia of the thyroid is one of the symptoms of hypothyroidism and of myxedema, so is it one of the common symptoms associated with Graves' disease; but is it not absurd to employ the same meager evidence to explain lowered oxygen metabolism in one disease and increased oxygen metabolism in another?

In clinical experience, however, there is one thing that indicates that the hyperplasia of myxedema and the hyperplasia of Graves' disease have not identical biologic significance, and that is the difference in the promptness and rapidity with which the goiter of the two contrasted diseases subsides under the influence of iodin or thyroidin. The goiter of myxedema melts away with amazing rapidity and once gone does not return when treatment is employed; but the hyperplasia of Graves' disease subsides more slowly and less completely and seems ready to spring into evidence again on slight provocation. Whatever the biologic provocation may be is unknown. The surgeon has no experience in the treatment of myxedema and seems therefore to be unembarrassed by the behavior of the thyroid in this disease in making his interpretations of the thyroid behavior in Graves' disease.

In myxedema we also see cardiac enlargement and arrhythmia which promptly subsides when thyroidin is administered, but the same cardiac symptoms in Graves' disease are not so amenable to thyroidin treatment but may be uninfluenced although the hyperplasia of the thyroid reverts to the colloid state.

Men write very freely about the excessive flow of internal secretion from a hyperplastic thyroid into the circulation, but this is certainly not true in myxedema and it has never been proved to be true in Graves' disease. In fact no one has thus far offered anything but inferential or fancied evidence for hyperthyroidism, and that has been so feeble it will not stand critical inspection.

**Toxic Adenoma.** Toxic adenoma is another bit of fancy that has got into the literature on the subject and has served to confuse the problems of the thyroid gland. The toxic part of the so-called

adenoma has never been proved nor has there been the slightest acceptable evidence for the existence of the supposed poison. Moreover the adenoma forms acini that hold iodin-containing colloid. In other words, these cells (so far as we know) perform the same function as the other thyroid cells. Why should we call this group of cells an adenoma if they perform the normal thyroid function? So far as I can learn the only reason for suspecting these aggregations of cells may be functionally differentiated from the rest of the thyroid is their want of lobulation. This is an anatomical difference from other portions of the gland that seems very insignificant compared with the features they have in common with the rest of the thyroid. Patients with the socalled adenomata bear iodin therapy in the same manner as other patients who have thyroid hyperplasia and I fail to see how the adenomata complicate the problem of Graves' disease, nor can I discover any clinical evidence for differentiating between socalled toxic adenoma and Graves' disease. In my visits to other clinics where men were trying to make a clinical differentiation between Graves' disease and toxic adenoma I could see no good reason for the differentiation.

There certainly is no evidence for superfunction of the thyroid gland as a cause for Graves' disease. All the evidence seems to indicate that hyperplasia socalled is evidence for incompetence of the gland and is associated with hypofunction instead of hyperfunction.

The argument of the advocates for resection of the thyroid as a therapeutic measure that "our patients and we are both satisfied," may serve in pleading for justification of an enterprise in which the ethics of buyer and seller are concerned but criticism that goes no further will not advance scientific knowledge.

Certainly no one pretends to claim that amputation of a large portion of the thyroid gland cures Graves' disease. The most that one dare claim for the procedure is, that the patients are improved by the treatment. It cannot be claimed that amputation protects patients against recurring exacerbations of the symptoms. Were amputation a cure for the disease our patients should be liberated from their symptoms which should not return.

It is extremely difficult to evaluate a treatment that is supposed only to ameliorate the symptoms of a disease that is self limited and runs a course varying from six months to three years, and is subject to frequent remissions and exacerbations.

To say that resection of the thyroid gland "breaks the chain" in the symptoms adds nothing to our knowledge. The biologic significance of the "thyroid link" is not understood. At any rate the chain of symptoms returns just the same after the thyroid link is surgically removed, so whatever the catenation may be it is unbroken by the amputation.

For the past twenty years, many thousands of patients have been

subjected to surgical treatment for Graves' disease, but the scientific fruit from it all has been extremely small. Nearly all we know about the subject has come from other than surgical sources. The history of medicine shows that any therapeutic procedure that has remained long in doubt proved in the end to have no real value. If surgeons have been really curing their patients all these years they should certainly have contributed something to our knowledge of the subject.

When the cause of Graves' disease will have been learned, the present mass of literature on the subject will look just as foolish as the great volume of therapeutic literature now looks that flourished fifty years ago about the subjects of diphtheria, typhoid fever and diabetes.

## A BACTERIOLOGIC STUDY OF GALL BLADDERS REMOVED AT OPERATION.

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In the study of the bacteria of the gall bladder the organisms have usually been searched for in the bile or other contents and sometimes in gall stones. Rosenow, in 1916, and Brown, in 1919, reported work on the culture of tissue of the gall bladder. This work showed that culture of the bile alone does not always furnish reliable data with regard to the presence or absence of infection in the tissue of the wall of the gall bladder.

In the present study we have cultured a portion of the wall and a specimen of bile in a series of 200 gall bladders, except in the few cases in which no bile was obtained. Cultures of the centers of gall stones were also made in cases of cholelithiasis whenever suitable stones could be secured. Representative cultures showing a good growth were injected intravenously into animals, chiefly rabbits, and the gall bladder as well as other organs were carefully examined at necropsy.

**Method of Making Cultures.** After the gall bladder had been removed, together with the clamp attached to the cystic duct, it was placed in a sterile dish, covered with sterile gauze and wrapped in a sterile towel, and taken immediately to the laboratory for culture. The specimen then was given to the pathologist for diag-

nosis. In no instance was the specimen examined by the bacteriologist later than five minutes after its removal from the patient.

A modified technique similar to that described by Rosenow was used in making the cultures. A small area of the surface of the gall bladder was seared with a hot blade and pierced with a sterile Pasteur pipette, through which about 5 cc. of the bile or other fluid content of the gall bladder was aspirated for culture. Tall tubes of glucose-brain agar and of broth made with a pancreatic digest of horse muscle were each inoculated with about 1 cc. of the bile, and a narrow bottle containing 12 cc. of dextrose broth with the remainder.

The stones were washed twice with sterile physiologic sodium chlorid solution, seared in the flame or with a hot blade, opened with sterile scissors, and the material from the center removed with sterile scissors or pipette. This material was either crushed and inoculated directly into the tubes of medium, or ground in a sterile mortar with sterile sand and an emulsion made with sterile physiologic sodium chlorid solution for inoculation into the various mediums.

The wall of the gall bladder was cultured by removing with sterile scissors a portion varying in size from 1 to 3 cm., and placing at once in a bottle containing 90 cc. of sterile physiologic sodium chlorid solution in which it was thoroughly shaken to remove as much as possible of any contaminating bacteria that might be present on the surface. After further washing in a second bottle of the solution the tissue was transferred to a covered sterile mortar, cut into small pieces with sterile scissors and ground up with sterile sand. This was then emulsified in about 10 cc. of sterile physiologic sodium chlorid solution and the emulsion inoculated into the various mediums. In some cases other pieces of tissue were cultured without being emulsified.

The mediums inoculated included tall columns of glucose-brain broth in tubes, glucose-brain agar, dextrose broth in tall bottles, horse-muscle pancreatic digest broth in tall tubes, infusion of heart muscle, infusion of meat and usually also blood-agar plates. In some instances the medium was enriched by the addition of from 5 to 10 per cent ascitic fluid. Aërobic, partial tension and anaërobic cultures were made. To insure anaërobic conditions, the tall tubes of anaërobic mediums were heated thoroughly in boiling water to drive off the dissolved oxygen and cooled and layered with paraffin oil or petrolatum immediately after inoculation.

After twenty-four hours of incubation at 37° C., cultures showing signs of growth were examined microscopically, and cultures showing a good growth were subcultured and used for injection into animals. From the shake cultures in soft agar it was usually possible to estimate the number of colonies present. The cultures showing no evidence of bacterial growth in twenty-four hours were incubated

for another twenty-four hours and reëxamined in the same way. In some instances the cultures remaining negative after forty-eight hours were incubated for from three to seven days longer, and the cultures made of unemulsified specimens in soft agar were kept for longer periods at room temperature.

**Results of Experiments.** Of the 200 patients, 67 were males and 133 females. The youngest patient was nineteen years and the oldest sixty-eight years of age, the average age being forty-three years; 167 were between the ages of thirty-one and sixty years. The duration of symptoms complained of varied from forty years to five weeks. The time elapsing since the last attack varied from five years to the time of examination, which was usually from one to three days before operation. This information was not obtained in all cases. Cultures were made from the bile of all but 7 of the 200 gall bladders. Positive cultures, chiefly bacilli and streptococci, were obtained from 28. Five of the bacilli were *Bacillus coli*, 1 was *Bacillus welchii* and 7 were unidentified bacilli. In the remaining 15 cultures streptococci were found, 2 in conjunction with staphylococci, 7 in conjunction with *Bacillus coli* or other bacilli and 6 in pure culture. The bile in which positive cultures were obtained was practically all light colored or entirely lacking in bile pigment, purulent, grainy or blood-tinged. Bile normal in color or darker than normal, "thick, dirty bile," afforded negative cultures in almost every instance. This is corroborative of Drennan's work, who proved experimentally that concentrated bile is an inhibitor to bacterial growth, and from the work of Johnson, who found that bacterial growth from the bile varied inversely to the concentration of bile salts. The condition of the gall bladders from which positive cultures were made from the bile was diagnosed by the pathologist as catarrhal cholecystitis in 5 cases, subacute cholecystitis with stones in 3 and chronic catarrhal cholecystitis with stones in the remainder. The organisms found in the bile were usually the same as those found in the wall of the gall bladder, and they were present in larger numbers than in the bile.

Gall stones were present in 107 of the 200 gall bladders. If only one stone was present, or if the stones were very small, none was cultured. However, in 67 cases the centers of the gall stones were cultured; in 43 the cultures were negative. Of the 24 positive cultures, 4 were considered contaminations, 2 contained *Bacillus coli* and 12 other bacilli, 2 of which were spore-bearing. Streptococci were found in 6 cultures, twice in conjunction with bacilli, and four times in pure culture. In 1 case in which the pathologist's diagnosis was chronic catarrhal cholecystitis with multiple stones, the gall bladder was very large, only slightly thickened and distended with light colored flocculent fluid with small, soft, putty-like stones. Such stones were also found in the common duct. Cultures of the stones which apparently were newly formed yielded

a few bacilli and large numbers of diplostreptococci, thus bearing out the belief that bacteria may be an important etiologic factor in the formation of stones.

Rosenow, in 1916, obtained positive cultures in 46 per cent of 62 stones examined; 27 per cent of these were pure cultures of streptococci. Of the 67 cases in our series, 31 per cent yielded positive cultures; 9 per cent yielded streptococci, 6 per cent in pure culture. The variation between our results as compared with those of Rosenow may be due to difference in technique. All of our earlier cultures of stones were made by inoculating directly into the culture mediums the flakes of material from the centers of stones. Recent cultures, made by grinding and emulsifying the nuclear material from the stones before inoculating the mediums appear to give a larger percentage of positive results, and no doubt if this method had been used throughout our series the number of positive cultures would have been greater.

Acute cholecystitis was not present in any of the gall bladders as operation was always postponed until the acute attack had subsided. In spite of the fact that gall bladders were removed, as a rule, during a quiescent interval, when it would be expected that the bacteria would be least active, and when the gall bladders were blue and the wall only slightly thickened, 98 of the 200 cultures from the wall yielded growths. Nine of the cultures yielded *Bacillus coli*, 2 *Bacillus welchii* and 13 unidentified bacilli. Staphylococci, or diplococci resembling staphylococci, were found in 17 cultures, and staphylococci with bacilli in 3. A large, round, green-producing diplococcus was found in 2 cultures and in 1 a pure culture of a diphtheroid bacillus. Twenty-six specimens yielded positive cultures of streptococci; 10 contained also *Bacillus coli* or other bacilli, while 16 were pure cultures. When it was known that the specimen had been exposed to contamination, either in the operating room or in the laboratory, or if the organism found was obviously saprophytic, the culture was regarded as contaminated and was not considered in the results. Twenty-five cases were regarded as contaminations.

The organisms appearing in largest numbers were usually streptococci, either in conjunction with a bacillus or in pure culture, although in two instances many pure cultures of Bacillus coli were found. If gall bladders were diseased grossly, bacterial growth was usually heavy. Such gall bladders were hyperemic or white and thick-walled. When gall bladders were blue and thin-walled, and a diagnosis of chronic catarrhal cholecystitis without stones had been made, bacteria were rarely found in large numbers; whereas 92 per cent showing heavy growth of bacteria contained stones; 3 (12 per cent) were diagnosed subacute cholecystitis with stones, and 20 (80 per cent) chronic cholecystitis with stones; only 3 of the latter were "strawberry" gall bladders.

**Results According to Pathologic Diagnosis.** The most common lesion found in the gall bladders was chronic cholecystitis with cholelithiasis (74 cases). Thirty-six (48 per cent) of these yielded positive cultures; in 16 streptococci either in pure or mixed culture were found. Of the 24 strawberry gall bladders with cholelithiasis, 5 (21 per cent) yielded a positive growth. Of the 59 gall bladders without stones but with chronic cholecystitis, 19 (34 per cent) yielded positive cultures. Five (21 per cent) of the 19 strawberry gall bladders yielded positive cultures. Of 16 cases of subacute cholecystitis, 7 (44 per cent) yielded positive cultures, chiefly streptococci and *Bacillus coli* alone or mixed.

**Results in Animals.** The material used for intravenous injection into rabbits was usually the original twenty-four-hour culture in glucose-brain broth or pancreatic digest broth of the wall of the gall bladder, bile or stone. The first dose varied from 3 to 8 cc., rarely higher, according to the size of the animal. Subcultures of the original strain were made into glucose-brain broth or into bottles of glucose or pancreatic digest broth. The subcultures in broth were incubated twenty-four hours, centrifuged, the supernatant fluid decanted and the remaining organisms suspended in a small volume of sterile physiologic sodium chlorid solution, in such proportion that 1 cc. of the suspension represented the growth from 10 to 11 cc. of broth. If the rabbits did not show symptoms within twenty-four or forty-eight hours after the first injection they were usually reinjected with from 3 to 10 cc. of the subculture in glucose-brain broth or from 1 to 6 cc. of suspension in physiologic sodium chlorid. Sometimes a third similar dose was given, and after an interval of from one to three days, any animals that did not die were anesthetized and examined for lesions.

Twenty strains isolated from the wall of the gall bladder, bile or stones were injected into 43 rabbits. Seven of these strains were secured from specimens of the 200 gall bladders. Thirteen addiional strains isolated from cholecystitic gall bladders have producedt similar results in animals and are included in this report.

Most of the strains injected into animals were streptococci, but 3 mixed cultures of streptococci and bacilli were injected into 5 rabbits. Cultures from the bile were negative in 1 animal; *Bacillus coli* was seen to the exclusion of any other organism in cultures from the bile of 2; streptococci and *Bacillus coli* were found together in 1 and a pure culture of streptococci in 1. The gall bladder or bile appeared diseased in 4 of the 5 rabbits, but usually the lesions were comparatively slight.

A pure culture of *Bacillus coli* isolated in 1 case of chronic catarrhal cholecystitis with stones was injected into 2 rabbits. Both rabbits died from the effects of the injection, 1 in twenty-four hours and 1 in seventy-two hours. The bacillus was cultured from the blood and the bile of both rabbits. One rabbit had an ulcer and

a hemorrhagic area on the greater curvature of the stomach, the lymph node draining the common duct was moderately enlarged and the bile was reddish brown. The other rabbit had no gross lesions, and apparently there was little localization of this strain in the gall bladder.

Animal experiments were made with a strain of *Bacillus typhosus*, isolated from a case not included in this series. Three years previously the patient had had an illness which was diagnosed elsewhere paratyphoid fever. Just previous to operation in the Mayo Clinic *Bacillus typhosus* had been isolated from the stools and from bile secured by duodenal drainage. *Bacillus typhosus* in large numbers was isolated from the slightly hyperemic and moderately thickened wall of the gall bladder removed at operation, from the golden-brown, slightly grainy bile, and from the center of one of the stones found in the gall bladder. Repeated injections of the original strain cultured from the wall of the gall bladder and of subcultures from this were made intravenously into 2 rabbits without any apparent untoward effect. Six injections, beginning with a dose of 4 cc. of the original culture in glucose-brain broth, and increasing to a maximum of 10 cc. of the subculture in glucose-brain broth, were made over a period of twenty-five days, yet neither rabbit showed any outward signs of disease or illness.

One rabbit that appeared well was chloroformed twenty-four hours after the sixth injection. It had a small, white gall bladder with markedly hyperemic vessels, especially at the fundus, and was filled with thick, slightly greenish, dirty, yellow pus. Several small abscesses were found in the gall bladder and in the lobe of the liver and one very small vegetative growth on a leaflet of the tricuspid valve. No lesions of the small or large intestines were found, and the spleen and kidneys appeared normal. Cultures of the kidney, spleen and blood were negative. An abscess in the liver yielded *Bacillus coli* and *Staphylococcus aureus* on culture and cultures of the bile yielded a moderate number of *Bacillus typhosus*.

The second rabbit continued to appear well, except that it began to lose a little in weight. Three weeks after the sixth injection it was found dead. The gall bladder was large, thin-walled and distended with watery fluid containing some flocculent material. The small bowel was slightly hyperemic, but no ulcerations were found. There were a few small hemorrhagic areas in the mucous membrane of the lesser curvature of the stomach, but the heart, kidneys, spleen, pancreas and urinary bladder appeared normal. Cultures from the spleen, kidney, liver and lymph node draining the common duct, and of mucus from the small intestines, were negative. Cultures of the heart's blood and one of Peyer's patches in the small intestine each yielded a few colonies of *Bacillus typhosus;* culture of about 1 cc. of the bile yielded about 300 colonies of *Bacillus typhosus*.

This is an interesting example of a typhoid bacillus with elective affinity for the gall bladder, and seems to show how the "typhoid carrier" state may be brought about in human beings. The bacillus apparently acquires elective affinity for the gall bladder, and once established in its tissues may grow and multiply for years, thus providing a focus for the dissemination of the bacillus.

Fifteen of the strains injected were streptococci in pure culture, usually green-producing on blood agar, although 4 were indifferent. Of 36 rabbits injected with pure cultures of streptococci, lesions of the gall bladder or streptococci in the bile, or both, were found in 27 (75 per cent). The streptococcus was recovered from the bile in 17 rabbits (47 per cent); the wall of the gall bladder was not cultured. Culture of the mesenteric lymph node draining the common duct yielded the streptococcus in 10 of 17 rabbits examined. Eight of the total of 43 rabbits injected had lesions of the heart, consisting chiefly of myocarditis and vegetative growths on the valve leaflets.

The lesions seen in the gall bladder varied greatly. In some animals the only changes were thickening of the wall of the gall bladder and sometimes discoloration of the bile, while in others the gall bladder was hyperemic or white and thick-walled, containing grainy, light-colored bile. Sometimes there were adhesions between the gall bladder and the liver, and in 1 case also localized peritonitis and marked fibrinous exudate.

**Summary.** Fourteen per cent of cultures of the bile from the gall bladder were positive. Cultures from normal or thickened dark bile were practically always negative; the positive cultures were from light-colored bile, usually grainy, purulent or blood-tinged. In other words, concentrated bile pigment is an inhibitor to bacterial growth, as found by Drennan, Johnson, Rosenow and others. Cultures of gall stones were positive in 31 per cent. In spite of the fact that the gall bladders were usually removed during a quiescent interval, often when there was no gross evidence of infection or inflammation, 49 per cent of the cultures of the wall of the gall bladder were positive. The organism most often found in the wall was a streptococcus, usually green-producing on blood agar.

Culture of the bile does not yield reliable data on the presence or absence of infection in the gall bladder. In our series only 14 per cent of the cultures of bile were positive. The streptococcus found produced lesions of the gall bladder or infection of the bile in 75 per cent of animals injected.

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## REFERRED PAIN IN GALL BLADDER DISEASES WITH A REPORT OF FOUR HUNDRED AND TWENTY-FOUR CONSECUTIVE CASES.

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Since Ross, in 1888, elaborated the theory of referred pain, much work has been done in attempting to interpret and correlate visceral sensory phenomena resulting from certain internal disorders. With the advance of modern medicine, authors, writing on this subject, have become more insistent and conclusive in their statements, and such assertions require attention, that they may be either disproved or accepted. We are concerned only with referred pain in gall bladder diseases, and shall attempt to elaborate some of the findings in a study of 424 consecutive cases of gall bladder diseases admitted to the first surgical or Cornell Division of the New York Hospital, service of Dr. Charles L. Gibson.

Henry Head, in 1893, had already recognized two types of pain of visceral origin: "One in the organ itself, which is more that of discomfort, and another in the surface of the body, which is a real painful sensation." Head also laid down the law of the location of visceral pain as follows: "Where a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility than that to which the stimulus was actually applied."

MacKenzie, writing on the viscerosensory reflex, admitted that: "From the viscus, an abnormal stimulus spreads beyond the sympathetic center and affects nerve cells in its immediate neighborhood. The cells so stimulated react according to their function, the sensory causing a sensation which the brain recognizes as pain and refers to the peripheral distribution of the sensory nerve in the skin or muscles, the motor producing contraction of muscle. The abnormal stimulation produces a portion of the cord abnormally irritable so that the tissues supplied by the nerves from that portion

of the cord are hyperalgesic, and attacks of pain, as in angina pectoris, are more easily provoked."

Pottenger says: "Sensory sympathetic fibers are found along with the motor sympathetic fibers in all structures, and when irritated the impulses are carried centralward where they are transferred to other neurones to complete reflexes in the skeletal structures. Therefore, every organ may generate stimuli which, if sufficiently strong, coursing centralward through the sympathetics, may result in reflex action in the skeletal structures through the spinal nerves which supply them. From physiologic facts we are led to assert that every important internal viscus is connected in the central nervous system through afferent *sympathetic* and efferent spinal nerves with definite skeletal structures, and, if inflamed, shows reflex sensory and motor activity."

Bechterew concludes that the sensory neurone gathers through its dendrites visceral stimuli and transmits them by way of its axis cylinders to Auerbach's and Meissner's ganglia, to the solar ganglia and to those of the gall bladder, and finally to the greater sympathetic, where on reaching the motor neurones, they are reflected and converted into motor impulses.

Arnau states that to any stimulus, in appropriate quantity or quality, the viscus should respond with an exaggerated reaction, and, depending upon the persistence of the stimulus, the reaction may express itself as hyperexcitability; fatigue, in the form of spasm or contracture; or functional insufficiency, temporary or permanent. At all events, the moment arrives when the nerve energy supplied to the affected organ cannot be totally or partially dissipated. Consequently, a state of hypertension follows in the corresponding portion of the sympathetic tract. For a certain length of time, or if the stimulus was not too intense or too unfamiliar, compensating discharges in other parts of the same or other portions are sufficient to dissipate the distorted energy. In other instances, other sympathetic mechanisms, as the vasomotor or the cutaneous glandular, are those that act as safety valves for the extensive tension due to the visceral conflict, but on other occasions, when the suddenness or greater intensity of the stimulus appear to be the predominating factor, the balance of the tension cannot be reëstablished before the accumulation of the centripetal energy in the corresponding spinal centers. In such instances, the energy, intensified by the extraordinary number of stimuli coming from the affected viscus and obstructed in its natural course to the sympathetic tract by the hypertension already existing in the latter raises in turn the potential in the somatic centripetal path. That increase in potential can only then be used in overexciting either the voluntary motor tract, producing spasms of variable intensity and duration (MacKenzie's visceromotor reflex); or the sensory tract, up to the point of causing, through the ascending paths, painful sensations, referred by the brain to the respective zones of the nervous

peripheral distribution, as if they originated directly from the latter (MacKenzie's viscero-sensory reflex). The remaining disturbances in the inner lining of the body or in the parenchyma, caused by the foreign agent, become sources of abnormal stimuli which, if persisting bring about manifestations of different character in the external body wall; hyperalgesic zones (Livingston), with or without underlying spasm; regional vasomotor, secretory and trophic disturbances (Arnau).

Arnau not only bears out the valuable clinical observations of Head, MacKenzie, Pottenger and others, but he also states that the natural role of the musculature of every hollow organ is to react on its contents and make them progress. That progress is subject to chronologic laws, the fulfilment of which is a requisite of health. As soon as an obstacle of any kind opposes the rhythmic or periodic movements necessary for such progress, irregular and more or less violent muscular contractions are produced. If the obstruction is so sudden, that it is not checked with equal rapidity by the sympathetic defenses, the somatic ones are aroused, and, by the mechanism proposed above, send the painful impulses to the brain as signal of distress.

According to Livingston, the theory of viscero-sensory phenomena in gall bladder diseases is, in a word, as follows: the autonomic fibers are in synaptic relations with sensory nerves from the skin zone, the exact location of which has not as yet been definitely established, but which we think come mainly from the eighth and some from the ninth and tenth dorsal segments. The center for perception is in the brain, which interprets pain arising during biliary colic as coming from the periphery or skin and not from the viscus itself.

Pain in gall bladder diseases, according to Rolleston, is due to two factors: first, acute inflammation of the gall bladder *per se*, and second, muscular spasm set up by the presence of the calculus in the duct. The pain in cholecystitis varies according to whether or not there is a stone attempting to pass along the cystic duct. When there is a stone, the pain is generally localized to the region of the gall bladder, or if there be contiguous peritonitis, adhesions, or bands (as is not uncommonly the case) the pain may be diffused over the right side, and even to the chest or to the left side. If the liver and gall bladder are much enlarged downward, the pain may extend down to the iliac fossa and even down to the lower extremities. When there is a stone in the neck of the gall bladder or in the cystic duct, the pain radiates also to the area beneath the inferior angle of the right scapula. This corresponds to the level of distribution of the eighth dorsal segment from which the gall bladder derives its main nerve supply. In uncomplicated cases, pain is not felt in the right acromial or clavicular regions, but in the right hypochondrium or in the epigastrium alone. Pain solely on the left side of the abdomen may be explained by the findings of Billings,

Beck, Kilgore, Robson, and others. Such pain is usually due to adhesions, traction of subperitoneal tissues, bands, or transposition of viscera. We have five cases with pain in the left side.

The paroxysmal nature of the pain bears out the observations and conclusions of MacKenzie, Pottenger, Arnau and other authorities, namely, that this is caused by the spasmodic contraction of the musculature of the gall bladder or ducts, due to attempts of the latter to expel the impacted calculus which is setting up the irritation. Severe pain has been described as lasting for days, but this is probably due to a succession of attacks supervening rapidly, with slightly less pain, due to the inflamed or distended gall bladder, in intervals between the more severe paroxyms.

Of the 424 cases on which this study is based, there are 10 without symptoms of pain. The passage of "silent" stones is not uncommon and both of these two conditions can be explained by quoting experiments done by Brüning and Gohrbandt: "Pain is only caused by the mucous membranes in animals when the irritation leads to intense muscular contractions. The contraction pain is undoubtedly initiated in the intestinal wall; and by assuming that the pain is caused by the instrumentality of the sympathetic, its special quality is explained. By numerous experiments with oil of mustard it was shown that after stroking or brushing, the mucosa pain results only on strong contraction of the muscular wall. As soon as muscular spasm develops and until it dies away, there is clear evidence of pain, and unless this motor reflex occurs, there is never pain."

Now we can readily understand MacKenzie's conclusion: "The violent stimulation of the spinal cord may leave after its subsidence an irritable focus in the cord rendering the portion of the cord more susceptible to stimulation, so that it becomes easier for future attacks of angina pectoris to be provoked. The irritable focus can be demonstrated to exist in some patients by the hyperesthesic state of the skin and muscles and other subcutaneous tissues in the region where pain is felt."

That such areas of hyperesthesia do occur in acute biliary disease was well borne out by the findings of Livingston, who emphasizes tests for local cutaneous hyperesthesia as part of a routine physical examination for the diagnosis of acute biliary disease. Of his 50 cases, with but 2 exceptions, all tested patients have positive cutaneous hyperesthesia. Of the 2 negative patients, 1 had both gall and kidney stones as concomitant findings and positive skin findings for nephrolithiasis was obtained. The other patient did not have acute colic but merely an increasing jaundice due to a stone.

In a review of the literature, we have arrived at the conclusion that pain in gall bladder disease is as variable as the pain in appendicitis. In other words, the pain may vary from an anginal type to one resembling that of a retroversion. Woolsey, in a series of 40 cases from the Second Surgical Division (Cornell), of Bellevue Hospital, gives the following figures regarding the sites of pain:

Ninety per cent had a more or less typical colic; 45.5 per cent had a pain radiating to the back alone; 18.5 per cent to the back and right shoulder; 5 per cent in the right shoulder alone.

The following charts represent the data obtained by us from the records of 424 consecutive gall bladder cases in the records of the New York Hospital (service of Dr. Gibson).

CASES OPERATED UPON AND IN WHOM THE DIAGNOSIS WAS MADE OR CONFIRMED AT OPERATION.

| | No. | Total, per cent. |
|---|---|---|
| 1. Pain in the right hypochondrium: | | |
| Not mentioned elsewhere | 87 | |
| Mentioned as "radiating" | 11 | |
| Not diagnosed as gall bladder disease: | | |
| No diagnosis | 1 | |
| Acute appendicitis diagnosed and found | 1 | |
| Acute appendicitis diagnosed and not found | 2 | |
| Strangulated hernia diagnosed and found to be due to a huge gall bladder | 1 | |
| Total with pain only in right hypochondrium | 103 | 24.4 |
| A. Pain in right hypochondrium and radiating to back: | | |
| Diagnosed correctly | 35 | |
| Diagnosed as acute appendicitis and so found | 1 | |
| Radiating to back and to right shoulder | 31 | |
| Diagnosed as intestinal obstruction or appendicitis and found to be a ruptured gall bladder | 1 | |
| Diagnosed as a kidney condition, pain radiated to right testicle | 1 | |
| Diagnosed as peritoneal adhesions, chronic salpingitis found | 1 | |
| Radiating to both shoulders | 3 | |
| Diagnosed as perforated gastric ulcer and not found | 1 | |
| Total with radiation to back or shoulder | 74 | 17.5 |
| B. Radiating to the epigastrium | 20 | |
| Diagnosed as acute appendicitis and so found | 1 | |
| No diagnosis | 1 | |
| With radiation to the right shoulder also | 8 | |
| C. Radiating to the lumbar region | 6 | |
| D. Radiating to the chest | 3 | |
| E. Radiating across the abdomen | 7 | |
| Diagnosed as gastric ulcer, but not found | 1 | |
| Also to the right side of the back | 3 | |
| F. Radiating to the right lower quadrant | 5 | |
| Diagnosed as acute appendicitis and so found | 1 | |
| Pathologic appendix found—not diagnosed | 3 | |
| G. Radiating to the left lower quadrant | 1 | |
| Grand total with pain in right hypochondrium | 237 | 55.8 |
| 2. Pain in the epigastrium: | | |
| Not mentioned elsewhere | 33 | |
| Not diagnosed as gall bladder disease: | | |
| No diagnosis | 1 | |
| Gastric ulcer diagnosed but not found | 3 | |
| Total with pain only in the epigastrium | 37 | 8.4 |

| | No. | Total, per cent. |
|---|---|---|
| A. Radiating to the back | 23 | |
| No diagnosis | 2 | |
| Gastric ulcer diagnosed, but not found | 2 | |
| Radiating to the right shoulder | 8 | |
| Radiating to the left shoulder | 2 | |
| Radiating to both shoulders and left arm | 1 | |
| Radiating to both shoulders and down | 2 | |
| Radiating to right shoulder and lumbar region | 1 | |
| No diagnosis; chronic appendicitis found | 1 | |
| Radiating to the lumbar region | 2 | |
| Total radiating to the back or shoulders | 44 | 10.4 |
| B. Radiating to the right lower quadrant | 7 | |
| Diagnosed as appendix and salpingitis; only slight congestion was found | 1 | |
| Retroversion diagnosed | 1 | |
| Radiating to the right lower quadrant and back—both cases were found to have adhesions of the gall bladder—in 1 this was diagnosed preoperatively | 2 | |
| C. Radiating to the heart | 1 | |
| D. Radiating to the sides | 2 | |
| E. Radiating to the left hypochondrium—diagnosed as gastric ulcer—adhesions and chronic appendix found | 1 | |
| Grand total with pain in the epigastrium | 96 | 22.6 |
| 3. Pain is given as "abdominal:" | | |
| Not mentioned elsewhere | 10 | |
| No diagnosis | 1 | |
| Gastric or duodenal ulcer diagnosed; not found | 3 | |
| Acute appendicitis diagnosed—not found | 1 | |
| A. Radiating to the back | 5 | |
| Salpingitis diagnosed and found with a pathologic appendix | 1 | |
| Radiating to the right shoulder | 1 | |
| Grand total with "abdominal" pain | 22 | 5.0 |
| 4. Pain in lower abdomen: | | |
| A. Pain in the right lower quadrant | 6 | |
| Had a pathologic appendix—not diagnosed | 4 | |
| Chronic appendix diagnosed and not found | 2 | |
| Chronic appendix diagnosed and found | 2 | |
| Chronic appendix diagnosed and found bound down | 1 | |
| Radiating to the back | 5 | |
| No diagnosis | 1 | |
| Salpingitis diagnosed and not found | 1 | |
| Salpingitis diagnosed and appendicitis found | 1 | |
| Appendicitis found—no preoperative diagnosis | 1 | |
| Radiating to right upper quadrant and left lower | 2 | |
| Acute appendix diagnosed and not found | 1 | |
| Acute appendix diagnosed and found congested | 1 | |
| Gastric ulcer diagnosed and not found | 1 | |
| Fibroids found—acute appendicitis diagnosed | 1 | |
| Total with pain in the right lower quadrant | 30 | 7.0 |

| | No. | Total per cent. |
|---|---|---|
| B. Pain in the left lower quadrant: | | |
| Salpingitis diagnosed; appendicitis found | 1 | |
| Salpingitis diagnosed; normal appendix and tubes | 2 | |
| Radiating to the heart | 1 | |
| Radiating to back—appendicitis diagnosed and found | 1 | |
| Total with pain in the left lower quadrant | 5 | 1.0 |
| 5. Pain in the stomach | 2 | |
| Diagnosed as gastric ulcer—not found | 1 | |
| Diagnosed as gastric ulcer—not found, but follow-up shows no relief after many years | 1 | |
| Found adhesions to the stomach | 1 | |
| Chronic appendicitis diagnosed and found | 1 | |
| A. Radiating to the back | 3 | |
| Definite duodenal ulcer seen at operation | 1 | |
| B. Radiating to the right shoulder | 1 | |
| Grand total with pain in the stomach | 11 | 2.5 |
| 6. Pain in the back | 3 | |
| A. Radiating to the right shoulder and upper back | 1 | |
| B. Radiating to the front | 2 | |
| 7. Pain in the chest: | | |
| A. Radiating to the back | 1 | |
| B. Radiating to both shoulders and abdomen | 1 | |
| 8. Cases with no pain: | | |
| Came to hospital for relief of mass in right upper quadrant | 1 | |
| Umbilical hernia | 1 | |
| Retention of urine | 1 | |
| General weakness | 3 | |
| Cough and choking | 1 | |
| 9. Bleeding from the vagina; no gall bladder symptoms; operated on for gynecologic condition | 3 | |
| Grand total of all cases operated on and diagnosis confirmed | 419 | 98.8 |
| Cases diagnosed as gall bladder disease but not operated upon—diagnosis not proved: | | |
| 1. Pain in the right upper quadrant only | 1 | |
| Radiating to the lumbar region | 2 | |
| Radiating across the abdomen | 1 | |
| 2. Pain in the epigastrium only | 1 | |
| Grand total of all cases summarized | 424 | 100.0 |

**Conclusions.** 1. Pain in gall bladder disease is a viscero-sensory phenomenon.

2. It is due mainly to two factors, namely:

(*a*) Acute inflammation of the biliary tract.

(*b*) Muscular spasm set up by the presence of calculi.

3. In the great majority of the cases the pain is in the typical text-book sites—thus it occurs in the right hypochondrium or in the epigastrium in 78.4 per cent of our cases. Radiation to the shoulder and back occurs in 27.9 per cent.

4. In our series there are 10 cases in which there was no pain—they having come to the hospital for other causes. This is probably due to a failure of, or insufficient irritation of the biliary tracts to cause muscular spasm. The presence or absence of areas of hyperesthesia was not stated as this was not tested routinely.

5. We must conclude that Woolsey's figures for typical pain are about correct, since to the 78.4 per cent with pain in the right hypochondrium and epigastrium we must add a goodly percentage of those with pain described as "abdominal," as this is probably due to an incomplete history that should have localized the pain more accurately. This would bring the percentage up to around 83 per cent, nearly approaching that of Woolsey.

We are greatly indebted to Dr. Nelson W. Cornell for the preliminary work done by him on these statistics, our summary of cases being merely a résumé of the abstracted records of the 424 cases as prepared by him. We are also indebted to Dr. Charles L. Gibson for permission to utilize and publish these figures and to the various members of the First Surgical or Cornell Division of the New York Hospital, whose cases have been herein reported.

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# A CLINICAL AND STATISTICAL STUDY OF CHRONIC ARTHRITIS BASED ON ELEVEN HUNDRED CASES.

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A statistical analysis of chronic arthritis from the clinical standpoint is herewith attempted, based on 1100 critically studied cases. During the war a similar study, together with laboratory observations, was carried out on soldiers in service, based on 400 cases.[1] Prior to the studies in the army and subsequently thereto, data have accumulated upon a series of cases seen and studied in civil life. It seems useful to consider together these two sets of data for the double purpose of the larger perspective afforded of arthritis as a whole, and the opportunity of contrasting certain features which might be expected to differ in the two groups. The total number of cases studied in civil life was 700. In presenting an analysis of such a large series certain points must be kept in mind. In the first place the study covers a number of years and reflects developments in the approach to the problem of arthritis, on the part of the writers at least. As a result of this, certain factors inadequately appreciated at the outset have assumed greater importance as more cases were observed and *vice versa*. Again, many cases were seen in consultation under circumstances which made difficult or impossible the collection of full data. Further, as the work progressed, new topics for scrutiny were included, which of necessity could then apply to subsequent cases only. The first half of the cases was studied without any fixed statistical plan other than that of careful clinical analysis from the standpoint of internal medicine. The subsequent cases were studied by means of a printed card bearing certain headings to be filled in. This latter method has the merit of preventing oversight of points of study, but is not highly elastic and tends toward the retention of data whose value may have become problematical. For these several reasons, therefore, this analysis is incomplete in some respects for the series as a whole, although in such instances the number of cases concerned was considerable and enough to justify emphasis. The civil cases are those seen in the office or in consultation, and those seen in the arthritic clinic, wards and private rooms at the Presbyterian Hospital Philadelphia.

Many of the cases could be differentiated as belonging to the proliferative or degenerative types of Nichols and Richardson. Some appeared to show features of both conditions and some cases could not be definitely classified under either head. Some antedated general recognition of this classification and could not be categoried from the records alone. In many cases the chief involve-

ment was in the muscular or tendinous structures and in some cases the outstanding symptoms were in the nervous system. Some cases represented such an early stage of development as to preclude classification. Insofar as differentiation of types could dependably be carried out, however, the classification of Nichols and Richardson was followed and the attempt was made to determine the incidence and the response to treatment of the proliferative and degenerative forms. While the classification of Nichols and Richardson is the simplest and the best now available, it is by no means final, as the authors of it frankly stated. There is room for doubt as to the wisdom of attempting too rigid separation into types in view of the limitations to our knowledge of the true nature of the arthritic and rheumatoid process *per se*. The cartilaginous and bony changes on which the above classification is largely based, represent an expression in these structures of a widespread process involving also the soft tissues and there is evidence that a common disturbance of physiology may underlie several clinical varieties of the disease.

The statistics presented under the caption "Progress" are comparatively meager for the reason that much time is required before the end result of treatment can be determined and during this period many cases disappear from observation. The whole study is limited to cases which could be personally observed throughout and no use has been made of the questionnaire system, as the effect of deformity or other secondary results form too complicated a picture for dependable analysis by the layman.

TABLE I.—NATURE OF ONSET IN 320 CIVILIAN CASES.

| | |
|---|---|
| Men in civil life | 216 |
| Women in civil life | 484 |
| Army cases | 400 |
| | 1100 |

An analysis of 536 cases of the civil group for age of onset reveals the following:

TABLE II.—AGE OF ONSET.

| Years. | Males, 159. | | Females, 377. | |
|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. |
| Below 10 | 4 | 2.5 | 9 | 2.4 |
| 10 to 15 | 9 | 5.6 | 15 | 4.0 |
| 16 to 20 | 19 | 11.9 | 29 | 7.6 |
| 21 to 25 | 12 | 7.5 | 21 | 5.5 |
| 26 to 30 | 14 | 8.8 | 38 | 10.1 |
| 31 to 35 | 15 | 9.4 | 45 | 12.0 |
| 36 to 40 | 22 | 13.7 | 44 | 11.6 |
| 41 to 45 | 16 | 10.6 | 54 | 14.4 |
| 46 to 50 | 15 | 9.4 | 55 | 14.7 |
| 51 to 55 | 12 | 7.5 | 27 | 7.2 |
| 56 to 60 | 6 | 3.7 | 27 | 7.2 |
| 61 to 65 | 10 | 6.2 | 12 | 3.1 |
| 66 to 70 | 2 | 1.3 | 1 | 0.2 |
| 71 to 75 | 2 | 1.3 | | |
| 75+ | 1 | 0.6 | | |
| | 159 | | 377 | |

Among civilians there were more than twice as many cases in women as in men, which is in keeping with the statistics of most observers. It will be observed that the greatest incidence of involvement in males is between the years thirty-six to forty, whereas in women it is between the years forty-one to fifty. There was a rather unexpectedly high incidence in males between sixteen and twenty years which is not far from the age of the army group previously studied.

TABLE III.—NATURE OF ONSET IN 320 CIVILIAN CASES.

| | Males, 95. | | Females, 227. | |
|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. |
| Acute | 43 | 46.2 | 94 | 41.4 |
| Gradual | 50 | 53.8 | 133 | 58.6 |

TABLE IV.—PRECIPITATING FACTORS IN 632 CASES.

| | Men, 70. | | Women, 162. | | Army, 400. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| Exposure | 30 | 42.8 | 19 | 11.7 | 232 | 58.0 |
| Dysentery | .. | .. | 2 | 1.2 | 33 | 8.2 |
| Injury | 9 | 12.8 | 17 | 10.5 | 30 | 7.5 |
| "Flu" | .. | .. | 6 | 3.6 | 28 | 7.0 |
| "Gas" | .. | .. | .. | .. | 23 | 5.7 |
| Drilling, hiking or overwork | 3 | 4.3 | 11 | 6.7 | 15 | 3.7 |
| Throat infections | 8 | 11.6 | 26 | 16.0 | 13 | 3.2 |
| Pneumonia | .. | .. | 2 | 1.2 | 6 | 1.5 |
| Neisser infection | 6 | 8.4 | .. | .. | 4 | 1.0 |
| Other infections | 7 | 10.0 | 8 | 4.8 | | |
| Alimentary | 4 | 5.7 | 11 | 6.7 | | |
| Mental strain | .. | .. | 14 | 8.6 | | |
| Menopause | .. | .. | 11 | 6.8 | | |
| Artificial menopause | .. | .. | 6 | 3.6 | | |
| Childbirth | .. | .. | 7 | 4.3 | | |
| Anemia | .. | .. | 2 | 1.2 | | |
| Operations | .. | .. | 3 | 1.8 | | |
| Sacroiliac strain | .. | .. | 1 | 0.6 | | |
| Chorea | .. | .. | 1 | 0.6 | | |
| Urticaria | .. | .. | 1 | 0.6 | | |
| Hay fever | .. | .. | 1 | 0.6 | | |
| Varicose veins | .. | .. | 1 | 0.6 | | |
| Use of radium | .. | .. | 2 | 1.2 | | |
| Unknown | 3 | 4.3 | 10 | 5.1 | 16 | 4.0 |

It will be observed that, in keeping with the army statistics, exposure played a surprisingly large role in the conscious experience of the men in civil life. In this respect, it is in full consonance with the role of exposure as a precipitating factor among soldiers, differing markedly from the small significance given to this etiologic factor among women. The nature of the exposure among the men was quite clear-cut, being referable to storms, wet feet, working in damp cellars and the like. The committee of the British Medical Association for the Prevention of Rheumatic Heart Disease among Children has laid great emphasis on exposure to dampness in houses

and elsewhere as an etiological factor.* Throat infections seemed to play a rather large rôle as a precipitating factor among women. In both groups, the onset of arthritis was gradual rather than abrupt in more than one-half the cases.

*Heredity.* Heredity or familial occurrence, including aunts and uncles: Of 142 patients carefully questioned on this point 83 gave a positive answer, 59 a negative. Hereditary predisposition seems to be a factor of generally unsuspected importance, being elicited in 58 per cent.

It would appear that in some families, especially those of asthenic or enteroptotic build, in whom one or two members had had arthritis, the occurrence of some phase of the syndrome in other existing members could almost be predicted, especially at or past mid life.

TABLE V.—DISTRIBUTION OF INVOLVEMENT IN 621 CIVIL CASES AND IN 400 ARMY CASES.

| | Males, 183. | | Females, 438. | | Army, 400. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| Knees | 119 | 65.0 | 298 | 68.0 | 248 | 62.0 |
| Hands | 86 | 46.9 | 296 | 67.5 | 58 | 14.5 |
| Spine | 95 | 51.9 | 173 | 39.4 | 54 | 13.5 |
| Shoulders | 77 | 42.0 | 161 | 36.7 | 127 | 31.7 |
| Ankles | 75 | 40.9 | 135 | 30.8 | 141 | 35.1 |
| Feet | 75 | 40.9 | 175 | 39.9 | 48 | 12.0 |
| Wrists | 59 | 32.7 | 121 | 27.6 | 47 | 11.7 |
| Elbows | 55 | 30.0 | 137 | 31.2 | 39 | 9.7 |
| Hips | 51 | 27.8 | 106 | 24.2 | 135 | 33.7 |
| Jaw | 26 | 14.2 | 79 | 18.0 | 3 | 0.7 |
| Arm muscles | 19 | 10.3 | 24 | 5.6 | 30 | 7.5 |
| All joints | 18 | 9.8 | 18 | 4.1 | | |
| Heels | 12 | 6.5 | 13 | 2.9 | 7 | 1.7 |
| Leg muscles | 13 | 7.1 | 25 | 5.7 | 89 | 22.2 |
| Sternocostal | 11 | 6.0 | 35 | 7.9 | | |
| Iliosacral | 10 | 5.4 | 39 | 9.0 | 16 | 4.0 |
| Thigh muscles | 9 | 4.9 | 13 | 2.9 | 28 | 7.0 |
| Sciatic nerves | 8 | 4.3 | 28 | 6.3 | 4 | 1.0 |
| Muscles of back | 6 | 3.2 | 7 | 1.5 | 33 | 8.3 |
| Sternoclavicular | 5 | 2.7 | 30 | 6.8 | | |
| All joints except jaw | 2 | 1.0 | 6 | 1.3 | | |
| Intercostal muscles | 1 | 0.5 | 7 | 1.5 | | |
| Intercostal nerves | 1 | 0.5 | | | | |
| Muscles of neck | .. | .. | 1 | 0.2 | | |
| Neuritis, arm | .. | .. | 8 | 1.8 | | |
| Neuritis, face | .. | .. | 2 | 0.4 | 1 | 0.3 |
| Sacroiliac | .. | .. | 3 | 0.6 | | |
| Coccyx | .. | .. | 1 | 0.2 | | |

A study of this table reveals that in all classes of arthritis the knees are the site of most frequent involvement although the hands are affected among women with practically the same frequency. It is to be observed also that the hands are involved among civilian men with a frequency much greater than was observed among

* J. Am. Med. Assn., 1926, **87**, 423.

soldiers in service. It is hard to explain this striking difference between the army and civilian groups, and it would appear to be referable to the greater chronicity in civil life, which allows of more widespread involvement, and also to the greater age of the subjects studied. In this last connection, can be mentioned the work of Goldschmidt and Light[2] who have called attention to "the presence of conditions" in the hands and fingers, "insuring a rapid flow of blood through tissues low in metabolism." This would help to explain the involvement of the fingers of men and women at or beyond mid-life at which time the age curve of metabolism undergoes a decline. Trauma and changes in environmental temperature may play a rôle and the use of the hands in washing may be a contributary factor in some women.

The lesser frequency of involvement of the hips as compared with the knees and ankles in all three groups may be partly explained by the fact of bearing less weight and by the fact that the hip is better protected from changes of temperature because of its deeper location and the thick highly vascular tissues covering it. The greater involvement of the feet among civilians as compared with soldiers is noteworthy and is probably referable partly to the frequently improper shoe lasts of civil life and partly to the elimination of most army recruits who showed foot weakness. The low incidence of involvement of the wrists among soldiers corresponds well with the low involvement of hands in the same group. Involvement of the spine and jaw is very much higher in civil life than in the army groups and the rarity of mandibular arthritis in the army was outstanding.

TABLE VI.—ANALYSIS OF 945 CASES IN REGARD TO FOCAL INFECTION.

| | Civilian men, 163. | | Women, 382. | | Army, 400. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| No foci found | 37 | 23 | 125 | 33 | 107 | 27.0 |
| Foci found | 126 | 77 | 257 | 67 | 293 | 73.0 |
| Tonsillar foci | 58 | 36 | 110 | 29 | 208 | 52.0 |
| Dental foci | 93 | 57 | 202 | 53 | 134 | 33.5 |
| Combined dental and tonsillar foci | 20 | 12 | 49 | 13 | 78 | 19.5 |
| Combination of foci other than dental or tonsillar | 41 | 25 | 57 | 15 | 38 | 9.5 |
| Genitourinary | 23 | 14 | 8 | 2 | 50 | 12.5 |
| Showing a combination of three or more foci | 16 | 10 | 22 | 6 | | |

Considering both civilian groups together, making 545 cases in all, demonstrable foci were present in 383 cases or 70 per cent. Among these 545 cases as a whole, dental infection was present in 295 cases or 54 per cent. Tonsillar infection was present in 168 cases or 31 per cent.

TABLE VII.—NUMERICAL RATIO OF VARIOUS KINDS OF FOCI TO THE TOTAL NUMBER OF FOCI FOUND.

| | Civilian men. | | Women. | | Army. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| Cases with foci . . . | 126 | | 257 | | 293 | |
| Cases with tonsillar foci | 58 | 46 | 110 | 43 | 208 | 71 |
| Cases with dental foci . | 93 | 74 | 202 | 78 | 134 | 46 |
| Cases with genitourinary foci . . . . . | 23 | 18 | 8 | 3 | 50 | 17 |

Other focal infections found were sinusitis, cystitis, otitis media, cholecystitis and gall stones, but the number of cases was small compared with the above.

In some cases where no foci were found, they had been eliminated before the subjects were referred by their previous physicians. It is to be noted, however, that these cases were still actively ill.

In view of the established etiologic role of focal infection in many cases of arthritis, full consideration has been given to it in this analysis. It can hardly be supposed, however, that all observed foci were equally, if at all, operative. Attention should also be drawn to an analysis for foci of infection in 100 consecutive admissions to the service of one of the present writers (R. P.),[4] in the general medical wards of the Presbyterian Hospital, Philadelphia. This was carried out in collaboration with Dr. B. A. Thomas, Dr. N. P. Stauffer, Dr. James E. Aiguier and their associates.

The leading disease states were nephritic and cardiac in the order named, arthritis coming third. Dental infection was present in 58 per cent; nose and throat infection, including sinuses, in 56 per cent; and genitourinary infection in 33 per cent. Infection of some kind was present in 87 per cent which is a higher proportion than is shown by the present series of arthritics (70 per cent).

Dental infection, therefore, occurs more frequently among male arthritics in civil life than it did among soldiers, the incidence of dental and nose and throat infections being practically reversed in these two groups. Dental infection also occurred more frequently in the 100 civilian cases of diverse diseases admitted to the hospital, 58 per cent, than it did in the army group of arthritics, 33.5 per cent, and with about the same frequency as in the civilian arthritics (54 per cent). In all groups genitourinary infections are the least common. The low figures for the army group, might have been referred to the examination of recruits and to instructions and prophylaxis, but the figures for the civilian men do not bear out this explanation and emphasize the more subordinate rôle played by genitourinary infections in the causation of arthritis. Among civilian arthritics, men suffered from genitourinary infections more frequently than did women and this corresponds well with the clinical impression of the writers that gynecologic infection plays a very

small rôle in the causation of arthritis among the many women so affected. The climacteric is apparently of much greater importance as an etiologic factor. This consideration again calls attention to the agencies other than infections which operate to produce arthritis or pave the way for it. The relative infrequency of causative gynecologic infection among women has also been pointed out by Dr. George M. Laws.[3]

These general figures should be correlated with the high incidence of recovery of arthritics in the army[1], in the presence of demonstrable foci, the number being about three times as great as that which improved after the removal of foci. In observing some cases over long periods of time, successive foci have been seen to develop, such as abscessed teeth, subsequent to the complete removal of such factors. In some such cases, the successive or coincident foci have been due to different organisms which strongly suggests a lowering of the normal defense mechanism as a whole. Furthermore, one of the present writers (R. P.),[4] has drawn attention to the fact that tissues, such as the tonsil, harboring foci, may undergo a marked transformation, losing their conspicuous character and becoming nearly or quite normal, following improvement in the arthritis from a well-planned regimen. These several considerations emphasize strongly the probability that focal infection may often be the result of a systemic imbalance as well as the cause of it. Nothing in these remarks is to be interpreted as minimizing the accepted importance of the recognition and removal of infections of all kinds in the treatment of disease. It is of the highest importance, however, to determine when and under what circumstances such infections arise and to ascertain the limits of their influence.

Complications in 484 civil cases. *Nervous.* In 139 male cases there were 109 nervous or circulatory distubances; in 345 women there were 358 nervous or circulatory manifestations. As several of these complications were often found in a single case the truth would not be reflected by expressing them in percentages of patients affected. Of these complications, the most outstanding were vertigo, tinnitus, cramps, twitchings and paresthesias. So frequently were these complications present that toward the end of the present series a special questionnaire was arranged on the examination cards with the following result:

The symptoms listed can mostly be referred by general clinical definition to the nervous system but it is possible that the circulation also may be concerned in the production of some. These symptoms obviously deserve consideration in relation to certain functional diseases of the nervous system and the conditions of their occurrence tend to throw light upon the nature of such disease. Attention has been previously called by one of the present writers (R. P.),[5] to this general relationship but the above figures have been forthcoming since then and further substantiate it. Some explanation

of the manner of their production is advanced in recent studies of arthritis[6] from the metabolic standpoint. Malignant neoplasms were very infrequent, which is significant in view of the ages of the civilian group. Active tuberculosis was very infrequent. This conforms to the experience of Dr. Lawrason Brown of Saranac Lake, who has kindly allowed us to quote his figures. He found only 11 cases of positive rheumatoid involvement among 4499 cases of tuberculosis.

TABLE VIII.—INCIDENCE OF NERVOUS SYMPTOMS.

| | Men examined. | Incidence of symptoms in question. | |
|---|---|---|---|
| | | No. | Per cent. |
| Tinnitus | 33 | 7 | 21 |
| Paresthesias | 33 | 12 | 36 |
| Twitching | 34 | 11 | 32 |
| Vertigo | 35 | 11 | 32 |
| Muscular cramps | 34 | 11 | 32 |
| Persistent headache | 139 | 15 | 11 |

| | Women examined. | Incidence of symptoms in question. | |
|---|---|---|---|
| | | No. | Per cent. |
| Tinnitus | 129 | 44 | 34 |
| Paresthesias | 118 | 69 | 58 |
| Twitching | 110 | 38 | 34 |
| Vertigo | 123 | 33 | 27 |
| Muscular cramps | 121 | 52 | 43 |
| Persistent headache | 345 | 41 | 12 |

In two previous communications[7, 11] one of the present writers (R. P.) has called attention to the fact that the combination of arthritis and severe diabetes is unusual. This impression was supported by the experience of E. P. Joslin and F. M. Allen and has since had further support from H. O. Mosenthal.[12] Recently Schmidt and Adams[8] have reported an incidence of 10.8 per cent of arthritis (51 cases) in a study of 474 diabetics. It is to be regretted that in their correlation, Schmidt and Adams did not observe the distinction pointed out that the comparatively mild diabetic behaves practically like a normal within the limits of his tolerance and that only in severe uninfluenced diabetes does carbohydrate fail to reach the tissues in important amounts. Under these circumstances much of the mechanism for the production of at least muscular "rheumatism" seems to be wanting and the writers have yet to see a case of nearly total or severe diabetes complicated by active rheumatic symptoms. Information indicative of such an occurrence would be appreciated by the present writers. In the present series of 700 civilian arthritics only 6 cases of diabetes were encountered and these were of a mild type, an incidence of 0.85 per cent.

TABLE IX.—STUDIES OF BLOOD PRESSURES IN 606 CIVILIAN AND ARMY CASES.

| Age, years. | No. cases. | Average blood pressure, mercury, mm. | | Highest. | | Lowest. | | Percentage.* |
|---|---|---|---|---|---|---|---|---|
| | | S. | D. | S. | D. | S. | D. | |
| **MALES, 339.** | | | | | | | | |
| 10 to 20 . . | 16 | 117 | 73 | 150 | 84 | 95 | 50 | 62 |
| 20 to 30 . . | 176 | 121 | 76 | 160 | 100 | 95 | 60 | 50 |
| 30 to 40 . . | 67 | 118 | 73 | 150 | 84 | 95 | 50 | 53 |
| 40 to 50 . . | 46 | 125 | 77 | 172 | 110 | 95 | 65 | 56 |
| 50 to 60 . . | 19 | 133 | 83 | 208 | 140 | 100 | 65 | 32 |
| 60 to 70 . . | 12 | 130 | 77 | 160 | .. | 110 | 60 | 50 |
| 70 to 80 . . | 3 | 146 | 74 | 150 | 55 | 140 | 92 | |
| **FEMALES, 267.** | | | | | | | | |
| 10 to 20 . . | 3 | 119 | 73 | 126 | 69 | 114 | 84 | 86 |
| 20 to 30 . . | 22 | 112 | 69 | 175 | 80 | 95 | 70 | 62 |
| 30 to 40 . . | 55 | 120 | 73 | 176 | 88 | 85 | 55 | 46 |
| 40 to 50 . . | 85 | 128 | 78 | 200 | 130 | 90 | 60 | 32 |
| 50 to 60 . . | 58 | 137 | 79 | 218 | 110 | 90 | 52 | 15 |
| 60 to 70 . . | 40 | 150 | 81 | 250 | 120 | 100 | 70 | |
| 70 to 80 . . | 3 | 141 | 76 | 165 | 90 | 126 | 65 | |
| 80 . . . . | 1 | 165 | 80 | | | | | |

* Of cases below 121 systolic.

Some of the lowest blood pressures were found in cases of advanced age with Heberden's nodes, corresponding in general to the degenerative type.

These tables show that the blood pressure tends to be normal or low among arthritics as a whole, high pressure being the exception rather than the rule. These findings are in keeping with those of Hench[9] for 320 cases and Swaim.[13] The number of cases in which a blood pressure of, say, 95 over 62 is found is surprisingly great. It is difficult to escape the belief that in many cases this low blood pressure tends to complicate the clinical syndrome and add to its refractory nature.

TABLE X.—ANALYSIS OF RED BLOOD COUNTS IN 700 CIVILIAN AND ARMY CASES.

| Red blood cells, per c.mm. | Males, 339. | | Females, 361. | |
|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. |
| 2,000,000 to 3,000,000 . . . . | 4 | 1.2 | 6 | 1.6 |
| 3,000,000 to 3,500,000 . . . . | 7 | 2.2 | 27 | 7.6 |
| 3,500,000 to 4,000,000 . . . . | 24 | 7.5 | 89 | 24.7 |
| 4,000,000 to 4,500,000 . . . . | 71 | 21.0 | 119 | 33.0 |
| 5,000,000 to 5,500,000 . . . . | 130 | 38.3 | 98 | 27.2 |
| 5,500,000 to 6,000,000 . . . . | 79 | 23.4 | 18 | 4.9 |
| 6,000,000+ . . . . . | 20 | 5.2 | 4 | 1.0 |
| | 4 | 1.2 | | |

There are 32 per cent of the men with less than 4,500,000 red cells.

There are 67 per cent of the women with less than 4,500,000 red cells.

It is an accepted fact that it is normal for women to have 500,000 fewer red cells than men.* There are 32 per cent of men with less than 4,500,000 red cells and 34 per cent of women with less than 4,000,000 red cells and the fact last mentioned may be one of the most important factors in the predominance of the female sex, 2 to 1, in arthritis.

Attention has been previously directed by one of the present writers (R. P.) to evidence indicative of a disturbance in the circulation, particularly in capillary areas, as productive of at least part of the pathology of arthritis and the rheumatoid syndrome (R. Pemberton[11,13]) (Pemberton, Cajori and Crouter[6]). The lower blood count of women would obviously tend to aggravate the effects of such a disturbance and make it operative earlier or more severely.

TABLE XI.—ANALYSIS OF 642 HEMOGLOBIN DETERMINATIONS.

| Hemoglobin, per cent. | Males, 289. | | Females, 353. | |
|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. |
| 40 to 50 | 1 | 0.4 | 3 | 0.8 |
| 50 to 60 | 8 | 2.6 | 12 | 3.5 |
| 60 to 70 | 14 | 5.1 | 47 | 13.2 |
| 70 to 80 | 35 | 12.1 | 123 | 34.4 |
| 80 to 90 | 86 | 29.6 | 111 | 31.6 |
| 90 to 100 | 104 | 36.0 | 56 | 16.2 |
| 100+ | 41 | 14.2 | 1 | 0.3 |

If 81 and over be taken as a normal per cent of hemoglobin, only 20 per cent of the men in contrast with 52 per cent of the women fall below this.

TABLE XII.—ANALYSIS OF WHITE BLOOD COUNTS.

| White blood cells. | Army, 400. | | Males, 142. | | Females, 342. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| 11,000 to 13,000 | 28 | 7 | 15 | 10 | 37 | 10 |
| 13,000 plus | 55 | 14 | 13 | 9 | 15 | 4 |

TABLE XIII.—PERCENTAGE OF POLYMORPHONUCLEARS.

| | Army, 178. | | Males, 109. | | Females, 299. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| Under 50 per cent | 14 | 8 | 10 | 10 | 14 | 4 |
| " 55 " | 37 | 21 | 21 | 20 | 36 | 12 |
| " 60 " | not noted. | | 33 | 30 | 65 | 21 |

This shows that a small percentage of cases had low polymorphonuclear counts, as observed also in the army studies, but in both series the differential counts were with this exception not far from the accepted normal range. The only other point of interest is a persistent eosinophilia of 5 to 8 per cent in several of the more severe hospital cases.

* Emerson, C. P.: Clinical Diagnosis, page 482, Lippincott Company, Philadelphia, 1913.

TABLE XIV.—DEFINITE, POSITIVE WASSERMANN REACTION.

| Army, 400. | | Males, 78. | | Females, 136. | |
|---|---|---|---|---|---|
| No. | Per cent. | No. | Per cent. | No. | Per cent. |
| 8 | 2 | 5 | 6.5 | 6 | 4.4 |

In the positive cases the luetic infection seemed to have no etiologic relation to the arthritis; and the suggested neglible rôle of syphilis among arthritics as a whole in this civilian series is in full consonance with the earlier findings among soldiers. This is not at variance with the occasional existence of arthritis of true luetic origin or with such conditions as Charcot's joints intercurrent to luetic disease of the central nervous system. The existence of Charcot's joints illustrates the operation of nervous influences as one of the factors in the production of arthritis.

TABLE XV.—PROGRESS (ABATEMENT OF ACTIVE PROCESS); 188 CASES IN CIVIL LIFE.

| | A. 100% | B. 75% | C. 50% | D. 25% | E. No. imp. | F. Grew worse. |
|---|---|---|---|---|---|---|
| *A. Foci Removed.* | | | | | | |
| 1. Removal of foci only | 2 | .. | .. | 1 | | |
| 2. Removal of foci plus tonic and physiotherapeutic treatment | 11 | 8 | 9 | 13 | 5 | |
| 3. Removal of foci, tonic and physiotherapeutic treatment plus lowered caloric intake | 13 | 16 | 8 | 7 | .. | 2 |
| 4. Removal of foci, tonic and physiotherapeutic treatment, lowered caloric intake and nonspecific protein or specific vaccine | .. | 3 | 1 | 1 | | |
| 5. Removal of foci and nonspecific protein or specific vaccine, with or without tonic and physiotherapeutic treatment | 1 | 1 | 2 | .. | 2 | |
| *B. No Foci Demonstrable.* | | | | | | |
| 6. Tonic and physiotherapeutic treatment | 3 | 4 | 1 | 3 | .. | 1 |
| 7. Tonic and physiotherapeutic treatment plus lowered caloric intake | 10 | 17 | 8 | 4 | 5 | |
| 8. Tonic and physiotherapeutic treatment, lowered caloric intake and N. S. P. or specific vaccine | .. | 1 | .. | 1 | | |
| *C. In Presence of Demonstrable Focus.* | | | | | | |
| 9. Tonic and physiotherapeutic treatment | .. | 1 | 3 | 1 | 1 | |
| 10. Tonic and physiotherapeutic treatment and lowered caloric intake | 6 | 6 | 3 | 1 | 1 | |

TABLE XVI.—PROGRESS IN ARMY CASES.

| 400 Army Cases. | No. | Per cent. |
|---|---|---|
| Recovered in apparent absence of demonstrable focus | 92 | 23.00 |
| Recovered in presence of demonstrable focus | 184 | 46.00 |
| Recovered after removal of foci | 34 | 8.50 |
| Improved after removal of foci | 31 | 7.75 |
| Unimproved after removal of foci | 28 | 7.00 |
| Recovered by "whatever" means | 310 | 77.50 |
| Improved by "whatever" means | 74 | 18.50 |
| Unimproved by "whatever" means | 16 | 4.00 |

For the reasons already mentioned, the statistics regarding progress appear comparatively meager, being based on 188 of the 700 civilian cases. This is not an inconsiderable series, however, if the time required for a true perspective of results be borne in mind. Some of the cases have been under observation for ten years or more. A more detailed analysis is contemplated of the results of treatment and other considerations in smaller groups of the 188 here considered.

Notwithstanding the important rôle of focal infection in many or most cases, the inadequacy of mere removal of foci in the treatment of arthritis required emphasis in the army studies and elsewhere and is increasingly obvious to students of arthritis. The inability to detect focal infection in many cases, after exhaustive collaborative search, and the betterment from various forms of treatment even in the presence of infection, made imperative in the present series the use of all forms of appropriate therapy. Every effort was made to analyze and treat each case upon its own merits, and there was no attempt to exploit any particular line of treatment. Much use was made of external measures such as physio- and hydrotherapy including colonic irrigation, postural exercises, etc. "Tonics," such as arsenic and strychnin were used when indicated. Low caloric feeding was frequently utilized in appropriate sthenic cases in which no focal infection could be found; in cases from which it had been removed; and cases which had not improved following this procedure. Nonspecific protein was used in various forms. The varieties of treatment adopted are not all indicated in the accompanying table as *those only are included* for which final figures were available.

Of the army cases 77 per cent recovered completely; of the civilian cases 24 per cent recovered completely. In the army only 4 per cent were unimproved; in the civilian 9 per cent were unimproved. These disproportions are to be expected in the presence of such long-standing cases as were often encountered in the civilian group and point to the hopefulness of treatment in rheumatic conditions when the syndrome is recognized early and treated intelligently. It is probably necessary to give large significance to the relative youth of the army cases and this implies that arthritis in young individuals should respond to treatment better than in older subjects, given equal degrees of severity and equal advantages of treatment.

For simplicity of analysis, the results of treatment were categoried in five groups A, B, C, D, E, and F, representing respectively, from the standpoint of cessation of the active arthritis, an improvement of 100, 75, 50, 25 per cent, failure of improvement and advance of the disease.

Thirty per cent of the civilian cases made an improvement of 75 per cent; 19 per cent made an improvement of 50 per cent; 17 per cent

made an improvement of 25 per cent. Thus, omitting those which were only slightly benefited, 73 per cent of all civilian cases were definitely improved or cured. This is an encouraging proportion in view of the refractory types presenting at this clinic, many of whom were referred after exhaustive treatment elsewhere; some after having been told that they could not be helped.

**Concerning Types of Arthritis.** Of 182 cases analyzed for progress and also for type of arthritis 77 were proliferative, 2 were questionably proliferative, 6 were degenerative, 12 were questionably degenerative, 1 was both proliferative and degenerative. In 94 cases the type of arthritis could not be determined.

Of 46 in Class A, who recovered completely by whatever means 17 were proliferative, 1 was degenerative, 2 were questionably degenerative, in 26 the type of arthritis could not be determined.

Of 58 cases in Class B., in which the improvement was 75 per cent by whatever means, 26 were proliferative, 2 were questionably proliferative, 1 was both proliferative and degenerative, 2 were questionably proliferative, 1 was both proliferative and degenerative, 3 were degenerative, 4 were questionably degenerative, in 22 the type could not be determined.

Of 35 cases in Class C, in which the improvement was 50 per cent by whatever means, 16 were proliferative, 3 were questionably degenerative, in 16 the type cold not be determined.

Of 29 cases in Class D, who made 25 per cent improvement, 11 were proliferative, 2 were degenerative, 3 were questionably degenerative, in 13 the type could not be determined.

Of 9 cases in Class E, in which no improvement was made by whatever means, 4 were proliferative, in 5 the type could not be determined.

Of 5 cases in Class F who grew progressively worse 3 were proliferative and in 2 the type could not be determined.

Of 50 cases selected because of a clear-cut improvement on a lowered caloric intake, 33 were proliferative, 6 were questionably proliferative, 1 was degenerative 3 were questionably degenerative, in 7 the type could not be determined.

Since compiling these figures, several more cases of the degenerative form have responded unmistakably to a lowered caloric intake. This is a strong argument for identity of etiology in some different types of cases and it also suggests identity of the underlying pathologic process.

The success which apparently attended treatment of the proliferative type in this statistical analysis, corroborates a long-standing impression in this clinic that this type respond better to treatment than does the degenerative, other things being equal. This will probably be at variance with the experience of some others but may be due to emphasis on different factors in treatment.

The proper treatment of arthritis constitutes one of the most

involved chapters in modern therapy. It necessitates long experience with the subtleties of the syndrome and a personal familiarity with many measures which, in the nature of things, cannot be adequately taught in the medical school, learned during the hospital internship or even acquired in the course of "general practice." The proper direction of such a measure as hydrotherapy or massage, for example, almost constitutes a specialty in itself.

A large measure of success can be expected only when the subject is approached, without bias for any fixed viewpoint or "panacea," and with an understanding of the physiologic disturbances involved. Arthritis touches more fields of medicine than does any other disease and deserves to be ranked as one of the major chapters of medicine, together with tuberculosis and syphilis.

A wider appreciation of these general considerations and more intensive study of the disease by the profession at large would bring about an inestimable reduction of suffering and economic loss on the part of society.

**Summary.** 1. A statistical analysis of 700 cases of chronic arthritis is presented from the clinical standpoint; comparisons are made with a previous study of 400 cases among soldiers, representing a different age group, making 1100 cases in all.

2. In civil life the onset of chronic arthritis was gradual in a little more than one-half of all cases.

3. The knee is the site of most frequent involvement among all groups and in both sexes although the hands are affected among women with practically the same frequency. The hands are involved among civilian men with a frequency much greater than was observed among soldiers in service. The reason for these differences is possibly to be found in the fact that the fingers are subject to trauma and environmental drops in temperature; that they are probably sites of relatively low metabolism and that the sharp decline of the age curve of metabolism in the older subjects tends to intensify these influences.

4. Foci are present in civilian arthritics with the same frequency as occurred among soldiers, viz: about 70 per cent. This is less than the incidence of foci in 100 consecutive cases of disease at large admitted to the medical service at the Presbyterian Hospital, Philadelphia.

5. The most frequent sites of focal infection in civilian arthritics were dental, nose and throat, and genitourinary in the order named. This is in contrast to the studies among soldiers who showed foci most frequently in the nose and throat (tonsils). Of these three regions, infection of the genitourinary tract is clearly least frequently the cause of arthritis in all three groups of cases, especially among women.

6. Symptoms referable to the nervous system were present with

surprising frequency and demonstrate the widespread influence of the causes of arthritis. This tends to throw light on the nature of certain diseases of the nervous system especially functional.

7. Malignant neoplasms were very infrequent, which is significant in view of the ages of the civilian groups.

8. Active tuberculosis was very infrequent. This conforms to the experience of Dr. Lawrason Brown, of Saranac Lake, who found only 11 cases of positive rheumatoid involvement among 4499 cases of tuberculosis.

9. Diabetes was met with in only 6 of the 700 civilian cases, an incidence of 0.85 per cent, and was of a mild type. The impression was confirmed that the combination of *active* arthritis or rheumatic myositis and *severe* uncontrolled diabetes is at least unusual.

10. The blood pressure tends to be normal or low among arthritics as a whole, especially toward middle life, though there are exceptions. In many cases it reaches strikingly low figures and probably contributes toward the refractory nature of the syndrome.

11. The normally low hemoglobin and red cell count of women as compared with men may be an important factor in the predominance of the female sex (2 to 1) in arthritis. The effects of this difference may be increased by the anemia common to this disease. This suggestion of the possible influence of the low red cell count and hemoglobin in women is in keeping with the evidence of disturbance of the vascular channels in arthritis elsewhere reported.

12. Of the army cases, 77 per cent recovered completely; of the civilian cases, which included the most advanced types, 24 per cent recovered completely. In the army only 4 per cent were unimproved; in the civilian group 9 per cent were unimproved. These differences are to be expected in view of the greater age of the civilian cases and the greater chronicity of the arthritis.

Omitting those cases which were only slightly benefited, 73 per cent of the civilian cases were definitely improved and of this proportion, one-third recovered completely. This is an encouraging result in view of the advanced and refractory types which contributed to the present series.

It emphasizes the importance of instituting vigorous treatment and justifies sustained and intensive effort. The impression still prevails in many quarters that arthritis is an incurable disease, whereas, in fact, there are few disease-states for which more can be done.

13. In view of the great prevalence and refractory nature of arthritis it deserves to be classed as one of the major chapters of clinical medicine. A more general familiarity with the subtleties of the disease and with the measures necessary for successful therapy would achieve a great reduction of suffering and economic loss on the part of society.

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## OBSERVATIONS ON THE BLOOD PRESSURE IN PULMONARY TUBERCULOSIS.

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The inquiry into the blood pressure in pulmonary tuberculosis dates back almost to the very inception of sphygmomanometry in clinical medicine. Available information shows that the credit for its earliest application in pulmonary tuberculosis is due to Marfan[1] whose extensive studies were probably the first to indicate the existence of a low systolic tension in phthisical subjects. He found low values in all but 3 per cent of such patients and expressed the belief that this is an early phenomenon in the tuberculous. Potain,[2] and later Teissier,[3] confirmed these observations and stated that a differential diagnosis between chlorosis and early tuberculosis could be made solely on the basis of the arterial tension, which is normal in the former and invariably low in the latter. Moreover, he felt that middle aged subjects who, although not suffering from cachexia or nervous exhaustion, showed a radial tension of less than 140 mm. of mercury should be considered tuberculous. Papillon[4] found that in patients admitted to hospitals for various diseases, a diagnosis of tuberculosis could be ventured on the basis of low arterial tension long before the appearance of constitutional symptoms and physical signs. Jumelais,[5] Boschi,[6] Bohland,[7] Gallavardin,[8] Burkhardt,[9] Pottenger,[10] Ingersheim,[11] Schkljar[12] and many others have also expressed themselves in support of the low arterial tension findings in phthisis pulmonalis.

More recently, the prognostic value of blood pressure determinations has received considerable attention. Careful studies have convinced Marfan[13] that the level of the arterial tension in the tuberculous is of greater prognostic value than pulse and temperature

observations. Whenever, he asserted, the tension is found high, it augurs a favorable prognosis, and when low, it indicates that the disease is not often amenable to treatment. Regnault,[14] Teissier,[15] Nauman[16] and others have come to similar conclusions as a result of extensive investigations.

On the other hand, the belief that low blood pressure is the rule in pulmonary tuberculosis has never remained unquestioned. Grandin[17] in 1899, observed that the arterial tension in the tuberculous may be above or below normal without any particular reason. Heusen's[18] patients presented figures within normal limits generally. Nauman[19] saw little difference in the blood pressure in comparable cases, between the normal and affected, and Neu,[20] N. J. Strangaard[21] and others are of similar belief, and in their recent and more exhaustive studies Betchov and Farbarg,[22] and Grant[23] came to similar conclusions. Moreover, Marfan[24] himself in a later study with "better technical advantages" has modified his own view now stating that in tuberculosis the blood pressure is normal and even above normal in 25 per cent of cases; and Betchov and others point to the valuelessness of low pressure findings as a prognostic index.

In view of this great divergence of opinion, it seemed worth while to study carefully the diagnostic and prognostic value of the sphygmomanometric findings in a group of 701 tuberculous patients, who were considered free from cardiorenal or metabolic disturbances. The average length of observation was slightly in excess of eight months.

The technique of the procedure cannot be discussed here from the theoretical point of view, but a few remarks are essential if the figures presented are to be correctly interpreted. The mercury manometer and the auscultatory method were used exclusively. The systolic reading was taken at the level of the mercurial column at which the first sound was heard at the bend of the elbow. The diastolic pressure was read at the moment of cessation of all sounds. Initial readings were discarded because of the effects of nervousness and apprehension of the patients in elevating the blood pressure. The figures representing pressure on admission were taken from the readings obtained a few days after the first examination. Subsequent blood pressures were taken every four to six weeks. In order to avoid the effects on the blood pressure resulting from changes of posture and the ingestion of food, the determinations of the arterial tension were made with the patient seated and approximately three hours after the morning or mid-day meal.

In the classification of patients, the rules of the National Tuberculosis Association were adhered to; and in view of the fact that most observers have paid little or no attention to the effect of age and sex on the blood pressure in the tuberculous, our tables were so arranged as to make possible the study of this phase of the subject as well.

TABLE I.—THE MEAN BLOOD PRESSURE IN RELATION TO AGE, SEX AND EXTENT OF INVOLVEMENT IN 701 TUBERCULOUS PATIENTS.

| Stage. | Age group. | Male. | | | Female. | | |
|---|---|---|---|---|---|---|---|
| | | Systolic pressure. | Diastolic pressure. | Pulse pressure. | Systolic pressure. | Diastolic pressure. | Pulse pressure. |
| I | 16–30 | 119 | 77 | 42 | 113 | 77 | 36 |
| | 31–40 | 119 | 81 | 38 | 117 | 79 | 38 |
| | 41–50 | 125 | 83 | 42 | 131 | 84 | 47 |
| II | 16–30 | 117 | 78 | 39 | 115 | 77 | 38 |
| | 31–40 | 117 | 77 | 40 | 123 | 81 | 42 |
| | 41–50 | 120 | 78 | 42 | 131 | 82 | 49 |
| III | 16–30 | 115 | 75 | 40 | 112 | 75 | 37 |
| | 31–40 | 116 | 76 | 40 | 115 | 77 | 38 |
| | 41–50 | 122 | 78 | 44 | 125 | 81 | 44 |

Table I shows the mean blood pressure in 701 tuberculous individuals in relation to the various age groups, sex and extent of involvement. The number of patients below sixteen and above fifty years of age was very small and they were, therefore, not included in this study. It will be noted that while there is a gradual lowering of the systolic pressure as the disease advances in the case of the male patients, the change is a very small one and in no instance exceeds 5 mm. The fact that the mean blood pressure of those in the forty-one to fifty age group, Stage II, is lower than that of the similar age group in Stage III, is probably due to the large number of fibroid cases among the latter who, as will be shown later, usually show higher pressure values. The increase in the blood pressure with advancing age is quite apparent.

In the females the advance of the disease as seen in Stage II seems to have no effect in lowering the blood pressure. In fact, the values in Stage II are higher than in Stage I and it is questionable as to whether this is entirely due to the larger number of fibroid patients among the females with Stage II disease than among comparable males. The lowering of the blood pressure in the female patients with Stage III disease is in conformity with the data obtained by most observers. An interesting feature is the comparatively higher systolic pressure in female patients in the forty-one to fifty age group regardless of the extent of their lesion. This corroborates the findings of Alvarez,[25] Lee,[26] Symmonds[27] and others in apparently normal individuals and is ascribed by many to the changes incident to the presence of, or the approaching menopause.

The mean diastolic pressure in the vast majority of patients increases with advancing age, the most marked advance being noted in incipient cases. On the other hand, the increase in the pulse pressure is noted particularly in the female patients over forty years of age.

TABLE II.—THE MEAN BLOOD PRESSURE IN RELATION TO AGE, SEX, EXTENT OF INVOLVEMENT AND ACTIVITY OF THE LESION ON ADMISSION IN 701 TUBERCULOUS PATIENTS.

| Stage. | Age group. | Number. | Male. | | | | | | Female. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Systolic pressure. | | Diastolic pressure. | | Pulse pressure. | | Systolic pressure. | | Diastolic pressure. | | Pulse pressure. | |
| | | | − Act. | + Act. | − Act. | + Act. | − Act. | + Act. | − Act. | + Act. | − Act. | + Act. | − Act. | + Act. |
| I | 16–30 | 32 | 119 | ... | 77 | .. | 42 | .. | 113 | ... | 77 | .. | 36 | |
| | 31–40 | 31 | 119 | ... | 81 | .. | 38 | .. | 117 | ... | 79 | .. | 38 | |
| | 41–50 | 27 | 125 | ... | 83 | .. | 42 | .. | 131 | ... | 84 | .. | 47 | |
| II | 16–30 | 149 | 118 | 113 | 76 | 75 | 42 | 38 | 117 | 113 | 78 | 75 | 39 | 38 |
| | 31–40 | 61 | 118 | 108 | 78 | 70 | 40 | 38 | 125 | 120 | 82 | 81 | 43 | 39 |
| | 41–50 | 33 | 121 | 111 | 79 | 81 | 42 | 30 | 132 | 124 | 82 | 88 | 50 | 36 |
| III | 16–30 | 215 | 117 | 112 | 75 | 74 | 42 | 38 | 114 | 111 | 77 | 74 | 37 | 37 |
| | 31–40 | 77 | 119 | 112 | 77 | 77 | 42 | 35 | 112 | 117 | 73 | 78 | 39 | 38 |
| | 41–50 | 76 | 123 | 118 | 77 | 78 | 46 | 40 | 131 | 120 | 84 | 79 | 47 | 41 |

Table II shows the mean blood pressure in the 701 tuberculous patients with relation to sex, age, extent of involvement, and activity of the lesion on admission. It will be noted that no figures for active patients in Stage I are given. This is due to the fact that only two such patients were found in this group and the blood pressure in both was within normal limits. The figures in the other groups show definitely higher systolic pressure values in patients with little or no activity than in those with moderate activity. The single exception is found in the case of female patients with Stage III disease in age group thirty-one to forty. Here those with active disease show higher systolic pressures than the inactive cases for no clear reason. However, the entire group consists of but 25 patients so that the chances for error are very great. The diastolic pressure is generally not much lowered in patients with active disease, but the pulse pressure is distinctly diminished in active cases, particularly in the advanced age groups.

TABLE III.—THE PROGNOSTIC VALUE OF BLOOD PRESSURE ESTIMATIONS AT THE BEGINNING OF TREATMENT IN 464 UNSELECTED CASES.

| Stage. | | No. | Male. | | Female. | |
|---|---|---|---|---|---|---|
| | | | Favorable, per cent. | Unfavorable, per cent. | Favorable, per cent. | Unfavorable, per cent. |
| II | Blood pressure above average for group | 119 | 89.8 | 10.2 | 80.5 | 19.5 |
| | Blood pressure below average for group | 76 | 78.2 | 21.8 | 72.0 | 28.0 |
| III | Blood pressure above average for group | 149 | 78.6 | 21.4 | 57.2 | 42.8 |
| | Blood pressure below average for group | 120 | 52.7 | 47.3 | 41.7 | 58.3 |

Analysis of Table III discloses the prognostic value of blood pressure estimations at the beginning of treatment in 464 unselected patients. It will be noted that both male and female patients whose initial blood pressure was above the mean for the group were more favorably influenced by treatment than those whose arterial tension was below the average for the respective age group. While only 10 per cent of male patients in Stage II whose blood pressure was above the average for the group progressed downward, the percentage of those with pressure below the mean was more than double or 21.8. In the case of the females, a similar situation existed. The percentage of progressive cases in those whose pressures were at or above the average for the group was 19.5 and in those below the mean, 28 per cent. It was not different in the case of patients with far advanced disease. Here the percentage of progressive cases in male patients with pressure value above the average for the group was 21.4 and in those with pressures below the average for the group 47.3 per cent. In the female patients, 42.8 per cent progressed downward in spite of blood pressure above the average for the group while 58.3 per cent did poorly with arterial tension below the mean for the group.

**Essential Hypertension in Pulmonary Tuberculosis.** Among these 464 patients, there were in all 46 with apparently essential hypertension, an incidence of about 10 per cent. In this group are included those patients whose blood pressure in age group sixteen to thirty was persistently above 135 mm. and above 140 mm. in the other age groups. These arbitrary figures are in accord with most authoritative views recently expressed and will be discussed later. It is noteworthy that among these patients the number with progressive disease was only 6, or 13 per cent as compared with 30 per cent progressive cases in the whole group.

TABLE IV.—THE INCIDENCE OF HEMOPTYSIS IN 763 TUBERCULOUS PATIENTS WITH RELATION TO SEX, AGE, EXTENT OF INVOLVEMENT, AND ARTERIAL TENSION.

| | Male. | | | | | | | Female. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage. | Total. | B.P. below mean. | | | B.P. above mean. | | | Total. | B.P. below mean. | | | B.P. above mean. | | |
| | | Number. | c̄ Hemopt. | | Number. | c̄ Hemopt. | | | Number. | c̄ Hemopt. | | Number. | c̄ Hemopt. | |
| | | | No. | % | | No. | % | | | No. | % | | No. | % |
| I | 54 | 22 | 1 | 4.6 | 32 | 2 | 6.2 | 41 | 17 | 2 | 11.8 | 24 | 1 | 4.2 |
| II | 168 | 69 | 12 | 17.4 | 99 | 16 | 17.8 | 93 | 39 | 5 | 12.8 | 54 | 4 | 7.5 |
| III | 240 | 96 | 37 | 38.5 | 144 | 37 | 25.7 | 167 | 69 | 35 | 50.7 | 98 | 14 | 14.3 |
| | 462 | | | | | | | 301 | | | | | | |

The relation of hemoptysis to the arterial tension has received considerable attention for many years, but because of the divergent views expressed, it seemed worth while to extend our inquiry to include also this phase of the subject. Cases with streaked sputum were not included in this group and only those with a definite history of having raised at least a teaspoonful of blood at any time during their illness are considered here. It was not thought advisable to study the blood pressure during or immediately after an attack of hemoptysis, so that our figures only show the incidence of hemoptysis in 763 patients with blood pressure at or above and below the average for the respective age groups, sex and extent of involvement. In the case of the male patients, it will be noted that hemoptysis occurred, as was expected, with greater frequency in those with advancing pulmonary involvement. However, hemoptysis occurred as often in those with pressures below the average for the group as in those with higher pressures. A similar condition obtained in the case of the females with moderately advanced disease, but in those with Stage III disease the incidence of hemoptysis was much greater when the arterial tension was below the mean for the group than in any other group. This was undoubtedly due to the fact that the female patients generally had a much less favorable prognosis than the comparable male patients, as can be learned from Table III, which shows that a grave prognosis could be expected in 58.3 per cent of the females as against 47 per cent in comparable males.

In the 46 patients with essential hypertension already referred to, hemoptysis was complained of by 7 only. Two of these had Stage II disease and 5 had advanced involvement. The 13 patients in this group who suffered from a minimal lesion disclaimed blood spitting at any time.

TABLE V.—THE ARTERIAL TENSION IN 62 PATIENTS WITH FIBROID DISEASE, IN RELATION TO SEX, AGE AND EXTENT OF INVOLVEMENT.

| Stage. | Age group. | Male. | | | Female. | | |
|---|---|---|---|---|---|---|---|
| | | Systolic pressure. | Diastolic pressure. | Pulse pressure. | Systolic pressure. | Diastolic pressure. | Pulse pressure. |
| II | 31–40 | 123 | 80 | 43 | | | |
| | 41–50 | 125 | 79 | 46 | 149 | 88 | 61 |
| III | 31–40 | 126 | 78 | 48 | 123 | 80 | 43 |
| | 41–50 | 122 | 74 | 48 | 138 | 84 | 54 |

While authentic data are meager, it is generally believed that the arterial tension in those with fibroid phthisis is higher than in those suffering from other forms of pulmonary tuberculosis. Our figures tend to support this view but unfortunately the number of fibroid

cases in our group is too small (62) to warrant definite conclusions. Table V shows almost invariably higher systolic figures than the mean for the entire group, while the diastolic pressure values remain relatively unaffected. The pulse pressure is, therefore, materially increased. This is particularly noticeable in the case of the women in the forty-one to fifty age group. Here the influence of the menopause in raising the arterial tension is to be taken into consideration.

TABLE VI.—PROGNOSTIC VALUE OF CHANGE IN BLOOD PRESSURE AS A RESULT OF TREATMENT IN 288 UNSELECTED CASES.

| Blood pressure. | Favorable. | | Progressive. | |
|---|---|---|---|---|
| | Number. | Per cent. | Number. | Per cent. |
| Stationary | 94 | 48.4 | 56 | 59.5 |
| Increased | 82 | 42.2 | 23 | 24.4 |
| Diminished | 18 | 9.4 | 15 | 16.1 |
| Total | 194 | .... | 94 | |

Changes in the blood pressure in the tuberculous with relation to the immediate prognosis were studied in 288 unselected patients, and are shown in Table VI. Of these none has remained under observation for a period shorter than eight months. The term "progressive" used in connection with these patients merely signified that rest cure was of no avail and that the prognosis as estimated on discharge was unfavorable. No patients in whom a rapid and fatal termination could be expected were included in this group and only persistent alteration in the blood pressure of at least 5 mm. were considered as indicating a change in blood pressure. It will be noted that the blood pressure remained stationary in 48 per cent of favorable and in 59 per cent of unfavorable patients, while an increase was observed in 42 per cent favorable and 24 per cent unfavorable patients. It is also noteworthy that in the favorable patients the arterial tension decreased in 9 per cent as compared with 16 per cent in those with a poor prognosis.

Among the 701 patients studied there were only 10 in whom tuberculosis and syphilis coexisted. The arterial tension in all but 1 patient was persistently above the mean for the respective group and of the 2 progressive patients, 1 had a persistently low blood pressure. Another patient with an aortic aneurysm and with an arterial tension of 160–110 was not included in this study.

Of the 15 patients who developed a pleural effusion, 8 had an arterial tension above and 4 below the average for the respective groups. The development of the effusion, whether it was on the right or left side, did not affect the blood pressure in either arm,

probably because large accumulations of fluid and consequent interference with the intrathoracic equilibrium were avoided by early and judicious aspirations.

There were among the patients studied, 39 with induced pneumothorax, 22 receiving treatment on the left and 17 on the right side. The arterial tension was at or above the mean for the respective sex, age and stage of the disease in 25 and below in 14. Among the former there were 3 progressive cases and among the latter, 4 had an unfavorable prognosis. In general the induction of pneumothorax had little if any influence in permanently modifying the arterial tension in the brachial artery on the homolateral or opposite side. This was probably due to the fact that only small quantities were given at each refill and mediastinal embarrassment was avoided as much as possible by carefully adjusting the intrathoracic equilibrium.

TABLE VII.—SHOWING THE EFFECT OF PNEUMOTHORAX REFILLS ON THE ARTERIAL TENSION IN 10 UNSELECTED CASES.

| Patient. | Sex. | Age. | Side treated. | Duration of treatment in months | Average inflation in cc. | Initial pressure. | Final pressure. | Mediastinal shifting. | Blood pressure before inflation (average). | Blood pressure ten minutes after inflation (average). |
|---|---|---|---|---|---|---|---|---|---|---|
| P. B. | F. | 26 | R | 3 | 400 | − 4 −2 | −2 −0 | Slight | 106–80 | 104–82 |
| H. S. | F. | 27 | R | 76 | 250 | −12 −8 | +18 +22 | None | 114–62 | 114–60 |
| M. M. | M. | 34 | L | 18 | 450 | − 8 −3 | +18 +20 | None | 108–76 | 110–74 |
| J. L. | M. | 34 | R | 18 | 450 | −12 −5 | −6 −0 | Slight | 112–80 | 112–82 |
| L. C. | F. | 15 | R | 13 | 550 | −5 −3 | −1 −0 | Marked | 92–62 | 100–62 |
| A. D. | M. | 30 | L | 78 | 225 | −4 −2 | +8 +16 | None | 118–82 | 120–80 |
| L. S. | M. | 21 | L | 9 | 300 | −7 −2 | −3 −1 | None | 106–74 | 106–74 |
| E. P. | F. | 34 | R | 11 | 400 | −8 −4 | +3 +7 | None | 108–82 | 106–84 |
| M. S. | M. | 29 | L | 24 | 425 | −8 −4 | −2 −0 | Slight | 120–72 | 120–72 |
| B. W. | M. | 36 | L | 26 | 250 | −6 −4 | +18 +22 | None | 122–82 | 122–84 |

Pressure figures represent readings of one arm of manometer therefore should be multiplied by 2.

Pressures below +10 = cm. H20; above +10 = mm. mercury.

In the 10 patients studied the effect of a refill on the arterial tension was found to be insignificant regardless of the final pressures so long as the mediastinal structures were not markedly displaced to the untreated side. In Table VII it will be noted that in patient L. C., who had a right pneumothorax, and in whom in spite of a zero final pressure marked mediastinal displacement occurred, there was a definite and recurrent increase in systolic pressure after each refill. In all others, no appreciable difference was noted in

spite of final pressure ranging between −3−1 cm. of water and +18+22 mm. of mercury.

**Discussion.** In the light of cold study, it appears that the widely held view regarding the low arterial tension in all phases of pulmonary tuberculosis is not supported by the results of careful investigation. It is noteworthy that the earlier observers labored under serious technical disadvantages with primitive instruments recording systolic pressures only. Moreover, the diagnosis of tuberculosis in its earlier stages was not possible as often in the past as it is today, with the result that the low pressure values observed in patients with advanced disease have been held to obtain in the early tuberculous as well. It is also noteworthy that the findings of many observers are greatly weakened by the fact that the sex and age of their patients, factors which have a remarkable influence on the arterial tension, were not taken into consideration in most of the earlier studies. There is another feature which tends to vitiate the findings of many observers and that is the great divergence of recorded opinions as to what constitutes the standard or normal blood pressure of an individual of either sex at a given age.

**Arterial Tension in Minimal Tuberculosis.** Gazes,[28] Papillon,[29] Regnault[30] and others were among the first to note the existence of low arterial tension in the tuberculous and considered it an early phenomenon of the disease, but they felt that a systolic pressure of 150 to 180 mm. was within normal limits; so apparently did Potain. While in a careful study of blood pressures in 9737 healthy University students and officers between the ages of sixteen and forty, the age period in which tuberculosis is most commonly recognized, Alvarez[25] found the arithmetical mean in the case of men at 125.5 mm. and in the case of women at 115 mm. The studies of Symmonds[27] on a vast number of accepted risks for the Mutual Life Insurance Company offer by far the most reliable index to the normal blood pressures in this country. He found that in males the average arterial tension is 124–81 mm. between the ages of fifteen and thirty, 125–83 mm. from thirty to forty and 127–84 mm. in the forty to fifty age group. The women averaged 2 mm. lower in both systolic and diastolic pressures until the age of forty and 2 mm. above the figure for the males after the age of forty. The New York Life Insurance Company in its "Instructions to Examiners," considers the normal blood pressure to be 120 mm. at twenty years, 123 mm. at thirty years and 126 mm. at forty years.

In this connection it is interesting to note the blood pressure findings in 171 patients who presented themselves for nontuberculous pulmonary complaints. This group includes many patients who for want of a better diagnosis are often placed in the category of neurocirculatory asthenia. Arranged in the same age groups as the tuberculous, their blood pressures as seen in (Table VIII) are almost identical with those found in patients with minimal tubercu-

lous disease. Most of these patients are of the type endowed with a poor respiratory apparatus in whom, as has been shown by Barach,[31] hypotension is to be expected.

TABLE VIII.—THE MEAN BLOOD PRESSURE IN RELATION TO SEX AND AGE, IN 171 PATIENTS TREATED FOR NONTUBERCULOUS PULMONARY COMPLAINTS.

| Age group. | Male. | | | Female. | | |
|---|---|---|---|---|---|---|
| | Systolic pressure. | Diastolic pressure. | Pulse pressure. | Systolic pressure. | Diastolic pressure. | Pulse pressure. |
| 16–30 . . | 118 | 78 | 40 | 113 | 77 | 36 |
| 31–40 . . | 121 | 83 | 38 | 119 | 80 | 39 |
| 41–50 . . | 123 | 79 | 44 | 125 | 81 | 44 |

Taking these data into consideration, the findings of Strangaard,[21] Betchov and Farbarge-Vail,[22] Grant[23] and our own appear to indicate that the arterial tension in incipient tuberculosis is not different from what we find in nontuberculous individuals of the same type, sex and age, and as a consequence blood pressure estimations are of no diagnostic value in minimal tuberculous disease.

**Arterial Tension in Advanced Disease.** It is different in the case of advanced disease. Here all evidence points to the fact that the systolic pressure decreases in direct proportion to the advancement and activity of the pulmonary process in both sexes and all age groups. This fall in arterial tension may be due to the dilatation of the peripheral vessels resulting from the absorption of tuberculotoxin as suggested by the work of Arloing and Guignard[32] in goats and dogs, Lævy[33] in the human and Emerson,[34] and possibly also to the direct action of the toxin on the heart muscle. Another contributing cause of the hypotension is tachycardia, which, as Henderson[35] and others have shown diminishes the systolic output of the heart by shortening the diastole. And it is also reasonable to suppose that the cardiac dislocation so frequently seen in advanced disease may in itself be partly responsible for this permanent depression in the arterial tension.

**Arterial Tension in Fibroid Phthisis.** The relatively higher pressure values in fibroid phthisis have long been noted. In such patients the tendency to sclerosis is not necessarily confined to the lungs. The arteries are often appreciably involved and the frequent association of chronic bronchitis and emphysema with this form of tuberculosis undoubtedly has some influence in raising the systolic pressure in patients so affected. The marked increase in both the systolic and pulse pressures in females with fibroid disease in the forty-one to fifty age group is particularly noteworthy and is at

least partly due to the influence of the changes secondary to the menopause.

**Relation of Arterial Tension to Hemoptysis.** There is a marked divergence of opinion regarding the relation of the blood pressure to hemoptysis. The early reports in the literature on the subject, particularly those of Strandgaard,[21] Muller[36] and Gallavardin[8] indicate a greater incidence of hemoptysis in those with high arterial tension. On the other hand, the studies of Walker,[37] Olivet,[38] Betchov,[22] and others coincide with ours in that they show that the incidence of hemoptysis is greater in those with low arterial tension. However, it is questionable whether the blood pressure is etiologically related to hemoptysis. It is a matter of common knowledge that the incidence of pulmonary hemorrhages increases with the advancement of the lesion and it is also well known that the progress of the pathologic process is responsible for the general devitalization as well as the fall in pressure. The two are, therefore, expressions of advanced disease. It is particularly noteworthy, however, that the incidence of hemoptysis in the tuberculous with essential hypertension is no greater, in fact somewhat lower, than in those with normal or subnormal arterial tension, thus further strengthening the belief that there exists no etiologic relation between hemoptysis and arterial hypotension.

**Prognostic Value of Blood Pressure Determinations in Tuberculosis.** Changes in the blood pressure of the tuberculous under treatment have been noted in Table VI. It appears that regardless of the immediate prognosis the blood pressure remains stationary in about 50 per cent of all patients, and although 42 of the patients with favorable prognosis show a persistent increase in the arterial tension, the blood pressure estimation alone is not a reliable indication of the immediate prognosis, because the pressure values increase in 24 per cent of definitely progressive patients. This view is also supported by the fact that the blood pressure actually decreases in 9 per cent of favorable cases and only 16 per cent of progressive cases.

On the other hand our findings are in agreement with those of Regnault, Nauman, Boschi, Betchov and others in that they show that the initial blood pressure estimations are of some prognostic value. In our study there were twice as many progressive cases among the male patients whose initial blood pressure readings were below the average for the respective group as among those with pressures at or above the average for the group, a ratio of 2 to 1. In the case of the women a similar condition existed although the difference was not quite so marked, the ratio being 3 to 2.

**Essential Hypertension in Pulmonary Tuberculosis.** The increase in the incidence of apparently essential hypertension is in no small measure due to the recently awakened interest in its early detection. Opinions differ as to what constitutes pathologic hypertension in

either sex at a given age. Janeway[39] was inclined to consider a systolic pressure of 150 to 160 as the upper normal limit, but later modified his view[40] and regarded pressures above 135 up to middle life and above 145 to 150 in later life, as indicating pathologic hypertension, if found on repeated examinations. Lee[26] places the upper normal limit at 140 and Alvarez[25] feels that the upper normal limit should be placed at 140 in men and 130 in women. The latter observer in an extensive study of apparently healthy University students and officers found an incidence of hypertension in 22 per cent of the men and 12 per cent of the women. Betchov[22] and his coworkers found hypertension in 29 per cent of his tuberculous patients but no mention is made as to the standards by which their cases were judged. Considered from the point of view of the data just referred to, the actual incidence of hypertension in their cases would seem not to exceed 8 per cent. In our study tuberculosis was associated with essential hypertension in 10 per cent of cases. The hypertension did not in any way tend to aggravate the pulmonary condition. On the contrary, the occurrence of hemoptysis and progressive disease in these patients was less frequent than in the whole group studied.

**Effect of Pleural Effusions and Pneumothorax Refills on the Arterial Tension.** The effect of the development of pleurisy with effusion or the induction of therapeutic pneumothorax, on the blood pressure in the homolateral or contralateral brachial artery was negligible so long as the intrathoracic equilibrium was not unduly disturbed as a result of the deflection of the mediastinum and its contents. The blood pressure remained unchanged in either brachial artery after pneumothorax refills regardless of the final intrathoracic pressure which in our cases with rigid mediastinal structures ranged between $-3-1$ cm. of water and $+18+22$ mm. of mercury. In cases with mobile mediastinal structures there was a definite and persistent increase in the systolic pressure which, however, returned to normal before the next refill.

Our experience is at variance with that of Cyriax[41] and others who observed higher pressure values on the side of the active lesion, the difference occasionally amounting to 26 mm. In patients with unilateral active disease or bilateral cases with activity apparently limited to one side, no appreciable and permanent difference in blood pressure was noted in the homolateral brachial artery. As a matter of fact the arterial tension in active cases on admission was almost invariably lower than in the inactive whether the homolateral or contralateral brachial artery was used in its determination.

The few patients in whom tuberculosis and syphilis coexisted had a higher arterial tension as well as a more favorable immediate prognosis than comparable patients free from this complication.

**Summary.** 1. The arterial tension in patients with minimal tuberculous disease is within normal limits for individuals of the

same sex and age. Blood pressure determinations are therefore of little or no diagnostic value in incipient tuberculosis.

2. The blood pressure declines with the advancement of the tuberculous process. Active cases almost invariably show a lower arterial tension than comparable quiescent patients.

3. Patients with fibroid disease apparently show higher pressure values than those with other forms of tuberculosis. This is particularly noticeable in women over forty and is probably secondary to the influence of the menopause.

4. The incidence of hemoptysis is greater in those with arterial tension below the average for their respective group than in those at or above the average. It appears, however, that the arterial tension and hemoptysis are not etiologically related. They are coincidental symptoms of advancing disease. Hemoptysis in the tuberculous with essential hypertension was seen less frequently than in cases with normal or subnormal blood pressure.

5. The few patients under observation in whom pulmonary tuberculosis and syphilis coexisted had a higher blood pressure and a more favorable immediate prognosis than patients free from luetic infection.

6. The development of an effusion and the induction of pneumothorax had no appreciable and permanent effect in altering the blood pressure in either brachial artery so long as the intrathoracic equilibrium was not unduly disturbed as a result of mediastinal displacement. The mediastinal dislocation was prevented by early and judicious aspiration in the case of effusions and careful adjustment of the intrapleural pressure in pneumothorax cases with labile mediastinal structures.

7. An increase or a decline in the blood pressure of patients under treatment does not offer a reliable indication as to the course of the disease. However, it appears that the initial blood pressure determinations are of some prognostic value. Those with higher arterial tension than the average for the age, sex and extent of involvement do better than those whose blood pressure is below the average for the group.

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## THE EFFECT OF SPECIFIC SUBSTANCES OF TUBERCLE BACILLI ON THE DIFFERENTIAL WHITE BLOOD PICTURE, SKIN SENSITIVENESS AND RATE OF SEDIMENTATION OF THE RED CELLS.

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In the course of the last years several laboratory methods have been proposed for the differentiation of the active and nonactive forms of tuberculosis. All these methods, (the sedimentation of red blood cells, precipitation reactions of the blood serum with nonspecific substances, specific complement-fixation reaction, autourine test, the examination of the qualitative white cell count) are a valuable help in certain cases. Although none of them gives a decisive evidence of the presence or absence of the activity of the

disease, some of these reactions, as the sedimentation of red blood cells, the precipitation with nonspecific substances, the qualitative white blood cell count, indicate probably important pathologic changes in the organism, the significance and mechanism of which are not yet understood. To investigate how these reactions are influenced by the administration of tuberculin is promising from several points of view. First, the administration of tuberculin can increase considerably the diagnostic or prognostic usefulness of the reactions. For instance, Grafe and Rheinwein[1] believed that very small doses of tuberculin have a great influence on the sedimentation of the red corpuscles in active cases of tuberculosis. On the other hand, the following of these reactions after the administration of tuberculin can reveal differences in the reaction of the patients which cannot be observed in the temperature curve, focal reactions, and so forth, which might have significance for the understanding of the pathologic relations, or might be useful in understanding the significance of the reactions themselves. We proposed in this work to study the changes occurring in the skin sensitiveness, in the sedimentation of the red blood cells, and the quantitative and qualitative white cell count. The skin sensitiveness indicates the specific tissue sensitiveness to the bacterial products. The sedimentation of the red blood cells indicates a change present in the blood plasma when tissue destruction occurs in the organism. It is often designated, although its mechanism is not known, as a colloid lability reaction, and it indicates probably the same changes in the plasma as the formerly mentioned nonspecific precipitation reactions in the serum. The quantitative and qualitative white cell count as it is generally known is in connection with the defensive mechanism against the infection and the qualitative white cell count the most sensitive indicator of the grade of the exhaustion of the organism. So studying these three phases, we hoped to obtain information from the most important aspects of the reaction of the organism against the infection.

To discuss in detail the very extensive literature on our subject is not warranted by the extent of our observations, and during the discussion of our results we will refer only to the papers which seem to us essential for their understanding.

**Experimental and Discussion.** The material which we have examined comprises 28 patients in different stages of the disease, which were the usual subfebrile or free from fever cases, and except in a few cases these have shown fair conditions. The specific therapy was given, and the von Ruck preparation (water and weak sodium hydroxide extract of the tubercle bacilli) was used, the initial doses usually being 0.0005 to 0.05 to 0.1 mg. dry bacilli substance. Although exact comparative investigations between the watery extract of tubercle bacilli and the old tuberculin were not made, we can say approximately that about 1 cc. of this water soluble bacillary

extract with 0.5 per cent dry organic material corresponds to the effect of 0.1 to 0.3 old tuberculin. This very approximate valuation is obtained from results on the skin of sensitive guinea pigs. A few patients proved to be very sensitive, and reacted markedly to even 0.005 mg. Some of the patients of this series had been under treatment for several months, and were receiving rather large doses, and to establish conditions relatively similar to those of the patients who were beginning treatment they received an increase in their doses. Due to different sensitiveness of the patients we could not select a standardized dose for our observations, but we used a dose which caused a perceptible local, general, or focal reaction. In our experience, while the reaction remains small, slight variations of doses do not change the direction of the response of the organism, and we suppose that the reaction obtained with different doses in different individuals remains comparable while the dose used is near to the smallest dose causing a reaction.

Our procedure was as follows: Every patient was examined three times in regard to the behavior of his skin sensitiveness, white blood formula, and rate of sedimentation, twenty-four hours before, during, and, as a rule, two or three days after the reaction following the subcutaneous injection of selected doses of the tubercle bacillus preparation. We observed the skin sensitiveness after intracutaneous application of a freshly made 1:50 to 1:250 and 1:1250 dilutions of a watery extract. After twenty-four hours we measured the size of the skin reaction. For the sedimentation test we used calibrated, uniform tubes, about 9 cm. long, with a mark at 6.5 cm. from the bottom, and of 0.5 cm. internal diameter. In the tubes we put 0.2 cc. 3.8 per cent sodium citrate solution, to which was added the freshly drawn blood, until it reached the mark (6.5 cm.), and mixed thoroughly with the sodium citrate solution by means of a glass capillary. The rate of sedimentation of the red cells was observed according to Westergreen in one, two and three hours. We considered the test as finished at the third hour, although we can confirm, as a rule, the observation of Morris[2] and Gaethgens and Goeckel[3] that the most significant differences occurred after two hours. To note a case as negative we would suggest being a little more liberal than is usual, and to follow the classification of Gaethgens and Goeckel, who extend the height of normal values in men to 15 mm., and in women to 20 mm., after two hours. After three hours these values are naturally a little higher, being in men around 15 to 17 mm., and in women 20 to 22 mm.

Our smears were obtained in accordance with the usual technique. At first we counted 200 leukocytes; later, using the socalled Meander method suggested by Schilling (moving the slide continuously, not in a horizontal or vertical direction, but in a continued horizontal-vertical zig-zag line like the ornamental Meander line) we counted only 100 leukocytes, 25 to 50 leukocytes on four distant squares

of the slide, controlled if necessary with counts of 300 to 400. After practice the experimental errors do not exceed 3 to 5 per cent. We made three whole white cell counts, and used the mean value. We used Schilling's[4] neutrophile formula instead of Arneth's formula, as we believe that for practical purposes the simplification of Schilling has great advantages. Instead of Arneth's 5 groups classified according to the number of their nuclei, Schilling suggests the distinction of only 3 types, according to the form of the nuclei, which together with the ancestor cell of the granulocyte system—the myelocyte—would make only 4 groups of cell types. According to Schilling the tendency toward polymorphism or segmentation is important, not the number of segments. The real significance of Arneth's work lies in the first class of his formula, that of the nonsegmented, nonpolymorphous nuclei, and the appearance of the cells of this type in the circulation during the infectious processes was confirmed by every investigator. Cells with segmented nuclei, no matter how many segments they may have, belong together as the ordinary type of the leukocytes, comprising the greatest part of them. Cells with nonpolymorphous, nonsegmented nuclei, with the form of the letters U, T, V, or halfmoon formed, or with the form of a ring, or rod-shaped (stabkernig) represent a younger type of cells, ripened without segmentation. These cells can be found in the circulation under normal conditions only in small numbers (3 to 5 per cent) and their number is increased by an infectious or toxic effect upon the bone marrow. The greatest part of Arneth's "shifting to left" is made up by these cells. The next group comprises cells with no tendency to polymorphism, having no curves, featuring a sausage or bean form. In normal blood these are very rare (0.5 to 1 per cent, juvenile). The last group is the granulated metamyelocyte. Registering these four types of cells from left to right in four groups, the first representing the myelocytes, the second the juvenile, the third the rod-shaped, (stabkernig) the fourth the ordinary cells with segmented nuclei, we have a scheme in which the decrease of cells from the fourth group toward the first means a shifting to left of the differential neutrophile formula.

To a certain extent the deciding point between an accidental fluctuation and a real change is an arbitrary one. In order to avoid an enforced interpretation of the results we decided to consider only an enlargement from 8 to 10 mm. of the skin reaction compared with a former one, as a real change of the sensitiveness.

In the case of the sedimentation, we interpreted as an acceleration due to the extract stimulation only changes over 5 mm. It is necessary to be very careful in explaining the small changes of the white cell count. We attribute a significance only when there are changes over 2500; in the differential formula of neutrophiles

and leukocytes, over 6 to 8 cells. We regard an eosinophilia to be over 5 per cent, a monocytosis, over 8 per cent, and variations over 2 to 3 cells to be a real change. In the neutrophile formula Schilling claims that cell-type III (stabkernig) is present in the normal blood up to four cells. We considered variations above 6 to 7 cells as a start toward shifting to left, as there are present in the normal blood 2 to 3 cells of Type II.

First we wanted to obtain information concerning the behavior of normal persons in regard to their skin sensitiveness, sedimentation test, and white blood picture after stimulation with the extract of tubercle bacilli. A certain doubt is always present as to when an individual is normal, especially in regard to tuberculous infection. We examined 9 normal control cases. Among these controls there were 6 men and 3 women. As one can see from Table I, we used different doses of extract according to the different sensitiveness of the individuals (from 0.008 to 0.2 mg.). In individuals who did not react to repeated small doses, the doses were increased until a reaction was obtained, as shown in Table I, cases Mr. L. and Dr. Fl.

Examining Table I, we see that among the 9 individuals 5 reacted with a moderate rise of temperature, only 1 with a higher rise, and 4 remained normal. The sedimentation test, measured after three hours, was normal, but very close to the borderline. Only in 1 case is there a real change in the speed of sedimentation (case Mr. K.) This man shows a lymphocytosis in his blood picture which is probably explained by previous treatment for tuberculosis, but now there is no clinical evidence of actual disease, and after seventy-four hours the sedimentation returns to the original value. After extract doses only in 1 case was there a real change in the skin sensitiveness (case Dr. S.) and this man has shown always a very marked hypersensitiveness to small doses of the extract, and had as a child a general lymphadenosis. We are under the impression that although there are great individual differences in the extent of the skin sensitiveness in normal persons, yet they have no real tendency to be influenced by application of the doses causing reaction.

Relating to the whole white count, in 5 of the cases there is a slight elevation of the whole white count, 12,000 to 15,000, which is mostly connected with the rise of temperature, but not always (Miss K.). Except in 2 cases, (Mr. O., Miss B.), the ordinary type of reaction in the differential white formula is an increase of neutrophiles and decrease of lymphocytes, without real change in the neutrophile formula after Arneth-Schilling. In only 1 case, (Miss G.), does the neutrophile formula show a tendency to be shifted, but it turned out that this individual several years ago, although now without symptoms, had some trouble, with her lungs. Two cases (Mr. O. and Miss B.) reacted in an opposite manner, with an

TABLE I.—BEHAVIOR OF NORMAL CONTROLS TO SPECIFIC STIMULATION.

● = CHANGE FROM THE NORMAL

| NAME | EXTRACT DOSE IN M.G. | TEMPERATURE | | | SUBJECT AFTER STIMULATION | SEDIMENTATION AFTER 3 HRS. | | | SKIN SENSITIVENESS. LARGEST AREA IN MM. | | | WHOLE WHITE COUNT | | | NEUTROPHILE FORMULA % | | | | LYMPHOCYTES % | | | MONOCYTES % | | | EOSINOPHILES % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BEFORE STIMUL. | 24 HRS LATER | 72 HRS LATER | | BEFORE STIMUL. | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL. | 24 HRS LATER | 72 HRS LATER | BEFORE STIMULATION | 24 HRS LATER | 72 HRS LATER | BEFORE STIMULATION | 24 HRS LATER | | | BEFORE STIMUL. | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL. | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL. | 24 HRS LATER | 72 HRS LATER |
| | | | | | | | | | | | | | | | I II III IV | I II III IV | | | | | | | | | | | |
| DR. S. | 0.025 | NORMAL | 100.4 | NORMAL | GENERAL MALAISE | 12 | 15 | 12 | 10 | ● 35 | 20 | 7600 | 15200 | 9000 | 61 | 0 ● 3 38 | 79 | 0 0 3 76 | 60 | 0 0 3 51 | 33 | 19 | 34 | 6 | 2 | 6 | 1 | 2 | 2 |
| DR. FR. | 0.008 | " | 99.2 | " | " | 14 | 17 | 13 | 20 | 20 | 20 | 7400 | 15000 | 8000 | 60 | 0 0 3 57 | 73 | 0 0 3 70 | 60 | 0 0 2 58 | 32 | 27 | 30 | 6 | 5 | 5 | 2 | 2 | 2 |
| MR. L | 0.15 | " | 98.9 | " | " | 14 | 14 | 14 | 10 | 10 | 10 | 9000 | 10000 | 8200 | 66 | 0 0 4 62 | 73 | 0 0 8 65 | 65 | 0 0 3 62 | 28 | 24 | 30 | 5 | 6 | 5 | 1 | 2 | 1 |
| MR. O. | 0.2 | " | 100.0 | " | " | 13 | 14 | 12 | 10 | 9 | 9 | 9200 | 16500 | 9000 | 57 | 0 0 3 54 | 43 | 0 0 3 40 | 58 | 0 0 3 55 | 35 | 46 | 32 | 0 | 4 | 2 | ● 7 | 7 | 7 |
| MR. K. | 0.1 | " | NORMAL | " | " | 17 | ● 28 | 19 | 3 | 7 | 4 | 8800 | 12000 | 9500 | 59 | 0 0 4 58 | 69 | 0 0 4 65 | 61 | 0 0 3 56 | ● 40 | 30 | 40 | 1 | 0 | 0 | 0 | 0 | 0 |
| DR. FL. | 0.1 | " | " | " | NONE | 19 | 20 | 20 | 15 | 15 | 15 | 7500 | 7500 | 8000 | 59 | 0 0 3 56 | 69 | 0 0 4 65 | 61 | 0 0 3 58 | 39 | 31 | 38 | 2 | 1 | 0 | 1 | 0 | 0 |
| MISS K. | 0.25 | " | " | " | | 25 | 29 | 23 | 15 | 13 | 12 | 7900 | 12800 | 8000 | 53 | 0 0 3 50 | 63 | 0 0 4 59 | 55 | 0 0 3 52 | ● 46 | 27 | 45 | 1 | 7 | 2 | 3 | 3 | 3 |
| MISS G. | 0.05 | " | 102.0 | " | | 21 | 22 | 20 | 8 | 5 | 7 | 9800 | 11800 | 8100 | 67 | 0 0 2 65 | 84 | 0 0 6 ● 78 | 65 | 0 0 2 63 | 27 | 14 | 28 | 4 | 2 | 2 | 1 | 0 | 2 |
| MISS B. | 0.1 | " | NORMAL | " | | 20 | 23 | 20 | 3 | 3 | 3 | 9200 | 10500 | 9000 | 60 | 0 0 2 58 | 45 | 0 0 2 43 | 60 | 0 0 3 57 | 33 | 54 | 35 | 5 | 0 | 2 | 2 | 1 | 2 |

elevation of lymphocytes, and an increase of neutrophiles after the extract injection. One of them had an eosinophilia (7 per cent. This case (Mr. O.) was a young man who several weeks previously had a bronchopneumonia which would explain his subsequent eosinophilia (as a sign of recovery after infection; feces examination for ova negative) and had also a bad intercurrent peridentitis, which causes lymphocytosis, according to Webb. He was examined for tuberculosis, and found without symptoms. His neutrophile formula was normal. The other case with an opposite reaction was a very stout young woman, and in her case perhaps some nervous or constitutional condition was responsible for her lymphocytic reaction. Her neutrophile formula was also normal.

A slight elevation in the white count, with an increase of neutrophiles and decrease of lymphocytes, without change in the neutrophile formula can be looked upon as the type of reaction of normal individuals after certain doses of the extract of tubercle bacilli. We shall emphasize the behavior of the neutrophile formula because in our experience we have hardly seen a real active case with normal neutrophile formula, only in cases showing improvement. The behavior of the eosinophiles and monocytes was rather irregular. All of our controls had more or less a general malaise after the administration of the extract.

In Tables II and III we combined the cases on admission (Table II) and those under treatment (Table III), classified both according to the different stages, and everywhere noted the anatomic state and the tendency of the disease. In the 28 cases we observed in 17 a more or less (sometimes remarkable) rise of temperature. This mostly parallels the change in sedimentation, but not always. There are cases where the temperature remains normal, and we could observe a real change in the sedimentation, and there are cases in which the sedimentation did not change, but we saw a little rise in the temperature. The same inconstancy is observed with the focal reaction. In all the 28 cases, the focal reaction was positive in only 10 cases, showing it to be less sensitive than the temperature, and, as we shall see, less sensitive than the sedimentation.

Concerning the sedimentation test we see from Table IV that there is a remarkable difference between the values of the first and second and the third stages, especially in the treated cases, higher values being mostly observed in the third stage and in the progressive types of the first and second. But by observation of the rate of sedimentation after a certain hour, we could not establish a fine differentiation between them. This is quite understandable because in a chronic infection like tuberculosis the pathologic processes are so complex that we are not justified in expecting a clear differentiation of the stages from the sedimentation test.

TABLE II.—BEHAVIOR OF PATIENTS ON ADMISSION BEFORE, DURING AND AFTER SPECIFIC STIMULATION.

| NAME | EXTRACT DOSE IN MG. | CLINICAL FINDINGS | SPUTUM | ANATOMICAL | TENDENCY OF THE DISEASE | TEMPERATURE: BEFORE STIMUL. | TEMPERATURE: 24 HRS LATER | TEMPERATURE: 72 HRS LATER | FOCAL REACTION | GENERAL REACTION | SEDIMENTATION: BEFORE STIMUL. | SEDIMENTATION: 24 HRS LATER | SEDIMENTATION: 72 HRS LATER | SKIN SENSITIVENESS LARGEST AREA IN MM.: BEFORE STIMUL. | SKIN SENSITIVENESS LARGEST AREA IN MM.: 24 HRS LATER | SKIN SENSITIVENESS LARGEST AREA IN MM.: 72 HRS LATER | WHOLE WHITE COUNT: BEFORE STIMULATION | WHOLE WHITE COUNT: 24 HRS. LATER | WHOLE WHITE COUNT: 72 HRS LATER | NEUTROPHILE FORMULA c/c: BEFORE STIMULATION | NEUTROPHILE FORMULA c/c: 24 HRS LATER | NEUTROPHILE FORMULA c/c: 72 HRS LATER | LYMPHOCYTES %: BEFORE STIMUL. | LYMPHOCYTES %: 24 HRS LATER | LYMPHOCYTES %: 72 HRS LATER | MONOCYTES %: BEFORE STIMUL. | MONOCYTES %: 24 HRS LATER | MONOCYTES %: 72 HRS LATER | EOSINOPHILES %: BEFORE STIMUL. | EOSINOPHILES %: 24 HRS LATER | EOSINOPHILES %: 72 HRS LATER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | | | | I II III IV | I II III IV | I II III IV | | | | | | | | | |
| **I STAGE** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mrs. T. | 0.1 | INF. BOTH UPPER LOBES | – | EXUDATIVE | SLIGHTLY ACTIVE | NORMAL | 99.4 | NORMAL | + | – | 27 | 33 | 29 | 20 | 20 | 22 | 8000 | 10000 | 9000 | 52 0 0 15 33 | 52 0 2 16 33 | 64 0 2 16 44 | 43 | 44 | 23 | 3 | 2 | 8 | 0 | 2 | 5 |
| Miss. U.Z. | 0.1 | DITTO | – | FIBROID | LATENT | " | 99.0 | " | – | – | 20 | 20 | 22 | 10 | 10 | 16 | 12000 | 15000 | 11000 | 60 0 0 9 51 | 48 0 0 8 40 | 58 0 0 11 47 | 39 | 47 | 37 | 5 | 3 | 4 | 2 | 2 | 2 |
| Mr. B | 0.1 | INF. BOTH APICES | – | DITTO | DITTO | " | 99.0 | " | – | ++ | 22 | 26 | 25 | 10 | 24 | 7 | 8000 | 10000 | 10000 | 54 0 0 5 49 | 70 0 2 8 60 | 51 0 0 5 46 | 42 | 46 | 46 | 3 | 0 | 2 | 1 | 0 | 1 |
| Miss Bo. | 0.05 | INF. BOTH UPPER LOBES | – | DITTO | STATIONARY | " | 99.0 | " | – | – | 25 | 26 | 26 | 0 | 12 | 22 | 11000 | 15000 | 12000 | 60 0 1 15 44 | 73 0 1 17 55 | 63 0 2 12 52 | 39 | 22 | 34 | 1 | 5 | 3 | 0 | 0 | 0 |
| Miss T. | 0.1 | DITTO | – | EXUDATIVE | SLIGHTLY ACTIVE | " | 100.6 | 99.0 | – | ++ | 37 | 34 | 36 | 9 | 30 | 20 | 15000 | 17000 | 14000 | 76 0 4 28 44 | 71 0 3 18 50 | 72 0 1 14 57 | 21 | 17 | 26 | 2 | 12 | 2 | 0 | 0 | 0 |
| **II STAGE** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mr. Br. | 0.05 | SMALL DESTRUCTIVE LESION R.U. INF. L.U. | + | FIBRO ULCERATIVE | ACTIVE | NORMAL | 101.6 | NORMAL | + | +++ | 25 | 25 | 25 | 10 | 20 | 10 | 11000 | 10000 | 10000 | 55 0 2 12 41 | 70 0 1 32 37 | 62 0 1 16 44 | 39 | 20 | 36 | 2 | 10 | 1 | 2 | 0 | 1 |
| Mrs. Hoo | 0.05 | INF. BOTH UPPER LOBES | + | FIBROID (LATENT) | LATENT | " | NORMAL | " | – | + | 29 | 29 | 30 | 4 | 12 | 10 | 12000 | 12000 | 10000 | 57 0 0 7 50 | 58 0 0 11 47 | 63 0 0 8 55 | 36 | 39 | 32 | 4 | 1 | 3 | 1 | 1 | 3 |
| Dr. W. | 0.02 | DESTRUCTIVE LESION R.U. | + | FIBRO ULCERATIVE | PROGRESSIVE | 99.0 | " | 99.5 | + | + | 37 | 38 | 39 | 10 | 20 | 20 | 12000 | 19000 | 14000 | 65 0 1 16 48 | 63 0 5 14 44 | 75 0 2 20 53 | 30 | 30 | 20 | 4 | 5 | 1 | 3 | 0 | 4 |
| Mr. C. | 0.0025 | OLD CAVITY R.U. LOBE INF. L.U. | – | DITTO | SLIGHTLY ACTIVE | NORMAL | 101.1 | NORMAL | + | +++ | 44 | 46 | 41 | 17 | 60 | 25 | 6000 | 26000 | 12000 | 65 0 0 7 58 | 85 0 0 34 51 | 74 0 0 23 45 | 24 | 12 | 18 | 2 | 3 | 3 | 9 | 0 | 5 |

TABLE II (*Continued*).—BEHAVIOR OF PATIENTS ON ADMISSION BEFORE, DURING AND AFTER SPECIFIC STIMULATION.

TABLE II (*Continued*).—BEHAVIOR OF PATIENTS ON ADMISSION BEFORE, DURING AND AFTER SPECIFIC STIMULATION.

| NAME | EXTRACT DOSE IN M.G. | CLINICAL FINDINGS | SPUTUM | ANATOMICAL | TENDENCY OF THE DISEASE | TEMPERATURES: BEFORE STIMUL. | TEMPERATURES: 24 HRS LATER | TEMPERATURES: 72 HRS LATER | LOCAL REACTION | GENERAL REACTION | SEDIMENTATION: BEFORE STIMUL. | SEDIMENTATION: 24 HRS LATER | SEDIMENTATION: 72 HRS LATER | SKIN SENSITIVENESS. LARGEST AREA IN MM.: BEFORE STIMUL. | SKIN SENSITIVENESS. LARGEST AREA IN MM.: 24 HRS LATER | SKIN SENSITIVENESS. LARGEST AREA IN MM.: 72 HRS LATER | WHOLE WHITE COUNT: BEFORE STIMULATION | WHOLE WHITE COUNT: 24 HRS LATER | WHOLE WHITE COUNT: 72 HRS LATER | NEUTROPHILE FORMULA %: BEFORE STIMULATION | NEUTROPHILE FORMULA %: 24 HRS LATER | NEUTROPHILE FORMULA %: 72 HRS LATER | LYMPHOCYTES %: BEFORE STIMUL. | LYMPHOCYTES %: 24 HRS LATER | LYMPHOCYTES %: 72 HRS LATER | MONOCYTES %: BEFORE STIMUL. | MONOCYTES %: 24 HRS LATER | MONOCYTES %: 72 HRS LATER | EOSINOPHILES %: BEFORE STIMUL. | EOSINOPHILES %: 24 HRS LATER | EOSINOPHILES %: 72 HRS LATER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **II STAGE** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mrs. E.A. | 0.01 | INF. BOTH UPPER LOBES | – | FIBROID | SLIGHTLY ACTIVE | NORMAL | 99.2 | NORMAL | – | + | 26 | 28 | 26 | 20 | 30 | 30 | 9000 | 10000 | 9000 | 42 | 64 | 52 | 50 | 33 | 43 | 8 | 3 | 3 | 0 | 0 | 2 |
| | | | | | | | | | | | | | | | | | | | | 0 0 6 36 | 0 0 4 60 | 0 0 4 48 | | | | | | | | | | |
| Mr. Gree | 0.025 | CAVITY R. UPPER | + | FIBRO-ULCERATIVE | ACTIVE | " | 99.2 | " | + | + | 40 | 40 | 36 | 22 | 13 | 20 | 15000 | 20000 | 15000 | 71 | 79 | 54 | 15 | 19 | 32 | 10 | 5 | 12 | 5 | 3 | 2 |
| | | | | | | | | | | | | | | | | | | | | 0 2 10 68 | 0 3 7 89 | 0 3 5 47 | | | | | | | | | | |
| Mr. Di. | 0.02 | INF. BOTH UPPER LOBES | – | FIBROID | SLIGHTLY ACTIVE | " | NORMAL | " | – | – | 13 | 15 | 11 | 11 | 14 | 28 | 10000 | 15000 | 11000 | 34 | 63 | 48 | 45 | 30 | 40 | 18 | 2 | 9 | 3 | 4 | 2 |
| | | | | | | | | | | | | | | | | | | | | 0 0 7 27 | 0 0 15 48 | 0 0 11 37 | | | | | | | | | | |
| Miss M. | 0.05 | SMALL CAVITY R.U. INF. L.U.L. | + | FIBRO-ULCERATIVE | PROGRESSIVE | 99.1 | 102.5 | " | + | + | 29 | 34 | 31 | 10 | 5 | 10 | 10000 | 15000 | 9000 | 74 | 76 | 71 | 22 | 20 | 21 | 4 | 4 | 3 | 0 | 0 | 6 |
| | | | | | | | | | | | | | | | | | | | | 0 5 29 46 | 0 7 33 36 | 0 4 24 48 | | | | | | | | | | |
| Mr. Gn. | 0.005 | DITTO | + | DITTO | SLIGHTLY ACTIVE | NORMAL | NORMAL | " | – | – | 31 | 37 | 32 | 10 | 10 | 10 | 16000 | 17000 | 15000 | 79 | 79 | 64 | 18 | 20 | 24 | 0 | 0 | 7 | 2 | 1 | 5 |
| | | | | | | | | | | | | | | | | | | | | 0 2 27 50 | 0 4 43 52 | 0 1 24 29 | | | | | | | | | | |
| **III STAGE** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mrs. W. | 0.003 | FIBRO-ULCERATIVE R.+ INF. L.U. | + | FIBRO-ULCERATIVE | SLIGHTLY ACTIVE | " | " | " | – | – | 31 | 43 | 43 | 12 | 18 | 18 | 18000 | 20000 | 17000 | 63 | 64 | 60 | 32 | 28 | 34 | 1 | 4 | 5 | 4 | 2 | 1 |
| | | | | | | | | | | | | | | | | | | | | 0 0 10 45 | 0 0 27 37 | 0 0 15 45 | | | | | | | | | | |
| Mrs. E. | 0.001 | CAVITIES BOTH UPPER L. | + | DITTO | ACTIVE AND PROGRESSIVE | " | 99.4 | 99.4 | + | + | 40 | 41 | 41 | 3 | 6 | 7 | 7000 | 16000 | 13000 | 55 | 70 | 58 | 40 | 12 | 40 | 5 | 14 | 2 | 0 | 0 | 0 |
| | | | | | | | | | | | | | | | | | | | | 0 0 21 31 | 0 3 38 29 | 0 2 28 54 | | | | | | | | | | |
| Miss Br. | 0.05 | SMALL CAVITIES R.U. INF. L.U. | + | DITTO | SLIGHTLY ACTIVE | " | NORMAL | NORMAL | – | – | 42 | 40 | 38 | 20 | 22 | 22 | 15000 | 21000 | 13000 | 70 | 80 | 69 | 14 | 13 | 27 | 15 | 5 | 3 | 1 | 2 | 1 |
| | | | | | | | | | | | | | | | | | | | | 0 2 28 42 | 0 4 36 40 | 0 0 11 58 | | | | | | | | | | |
| Dr. R. | 0.003 | SMALL CAVITIES BOTH U.L. | + | DITTO | ACTIVE AND PROGRESSIVE | 100.1 | 100.1 | " | + | + | 40 | 40 | 40 | 6 | 7 | 6 | 14000 | 21000 | 20000 | 73 | 73 | 70 | 16 | 18 | 16 | 7 | 8 | 8 | 4 | 2 | 3 |
| | | | | | | | | | | | | | | | | | | | | 0 3 19 51 | 0 1 28 43 | 0 1 29 40 | | | | | | | | | | |
| | | | | | | | | | + | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE III.—BEHAVIOR OF PATIENTS ON ADMISSION BEFORE, DURING AND AFTER SPECIFIC STIMULATION.

| NAME | DOSE IN MG. | EXTRACT | TIME OF TREATMENT | CLINICAL FINDINGS | SPUTUM | ANATOMICAL | TENDENCY OF THE DISEASE | TEMPERATURE: BEFORE STIMUL. | TEMPERATURE: 24 HRS LATER | TEMPERATURE: 72 HRS LATER | FOCAL REACTION | GENERAL REACTION | SEDIMENTATION: BEFORE STIMUL. | SEDIMENTATION: 24 HRS LATER | SEDIMENTATION: 72 HRS LATER | SKIN SENSITIVENESS LARGEST AREA IN MM.: BEFORE STIMUL. | SKIN SENSITIVENESS LARGEST AREA IN MM.: 24 HRS LATER | SKIN SENSITIVENESS LARGEST AREA IN MM.: 72 HRS LATER | WHOLE WHITE COUNT: BEFORE STIMULATION | WHOLE WHITE COUNT: 24 HRS LATER | WHOLE WHITE COUNT: 72 HRS LATER | NEUTROPHILE FORMULA %: BEFORE STIMULATION | NEUTROPHILE FORMULA %: 24 HRS LATER | NEUTROPHILE FORMULA %: 72 HRS LATER | LYMPHOCYTES %: BEFORE STIMUL. | LYMPHOCYTES %: 24 HRS LATER | LYMPHOCYTES %: 72 HRS LATER | MONOCYTES %: BEFORE STIMUL. | MONOCYTES %: 24 HRS LATER | MONOCYTES %: 72 HRS LATER | EOSINOPHILES %: BEFORE STIMUL. | EOSINOPHILES %: 24 HRS LATER | EOSINOPHILES %: 72 HRS LATER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *I* STAGE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Miss B. | 0.65 | 3 MOS. | INF. BOTH UPPER LOBES | – | EXUDATIVE | LATENT | 98.6 | 99.0 | NORMAL | + | – | 19 | 29 | 20 | 14 | 20 | 7 | 11000 | 10000 | 12000 | 51 | 33 | 32 | 45 | 43 | 40 | 0 | 2 | 1 | 4 | 2 | 5 |
| | | | *II* STAGE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Miss C. | 1.5 | 12 WKS. | INF. BOTH UPPER LOBES | – | EXUDATIVE | SLIGHTLY ACTIVE | NORMAL | 104.5 | NORMAL | + | ++ | 27 | 36 | 26 | 22 | 25 | 25 | 8000 | 10000 | 9000 | 53 | 65 | 51 | 40 | 30 | 45 | 3 | 0 | 0 | 3 | 4 | 3 |
| Mrs. He. | 0.4 | 12 WKS. | DITTO | – | DITTO | LATENT | " | NORMAL | " | – | – | 26 | 31 | 27 | 12 | 24 | 7 | 8000 | 8000 | 8000 | 42 | 50 | 48 | 44 | 39 | 42 | 1 | 3 | 0 | 1 | 4 | 0 |
| Miss Th. | 0.15 | 9 MOS. | DITTO | + | FIBRO ULCERATIVE | DITTO | " | " | " | – | – | 10 | 16 | 12 | 6 | 17 | 6 | 7000 | 9000 | 8000 | 55 | 55 | 60 | 38 | 30 | 39 | 5 | 4 | 5 | 0 | 10 | 3 |
| Mr. Su. | 0.3 | 5 MOS. | CAVITY R.U.L. INF. L.U.L. | + | DITTO | STATIONARY | " | 99.3 | " | – | – | 26 | 19 | 20 | 38 | 36 | 35 | 15000 | 18000 | 17000 | 48 | 47 | 45 | 44 | 43 | 45 | 1 | 1 | 1 | 3 | 9 | 9 |
| Mr. McN. | 1.6 | 8 MOS. | SMALL CAVITY R.U.L. INF. L.U.L. | + | DITTO | DITTO | " | 99.0 | " | – | – | 33 | 35 | 36 | 14 | 10 | 7 | 14000 | 14000 | 14000 | 51 | 62 | 55 | 37 | 34 | 38 | 4 | 0 | 4 | 3 | 4 | 8 |
| | | | *III* STAGE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mr. T. | 0.65 | 6 MOS. | CAVITY R.U.L. INF. L.U.L. | + | FIBRO ULCERATIVE | STATIONARY | NORMAL | NORMAL | NORMAL | + | – | 15 | 25 | 26 | 15 | 10 | 17 | 9000 | 8000 | 10000 | 65 | 76 | 68 | 30 | 14 | 30 | 4 | 5 | 5 | 0 | 4 | 1 |
| Mr. Be. | 1.3 | 13 MOS. | INF. R.U.L. CAVITY L.U.L. | + | DITTO | DITTO | " | 100.5 | " | + | ++ | 33 | 31 | 31 | 10 | 6 | 11 | 10000 | 10000 | 8000 | 45 | 85 | 50 | 45 | 13 | 40 | 5 | 1 | 6 | 4 | 1 | 6 |
| Mr. Su. | 1.4 | 3 MOS. | INF. R.U.L. SMALL CAVITIES L.U.L. | + | DITTO | DITTO | " | 98.1 | " | – | + | 33 | 35 | 34 | 0 | 11 | 8 | 13000 | 16000 | 16000 | 55 | 46 | 39 | 40 | 48 | 51 | 3 | 3 | 6 | 1 | 1 | 1 |
| Mr. Va. | 0.5 | 3 MOS. | SMALL CAVITIES BOTH LOBES | – | DITTO | SLIGHTLY PROGRESSIVE | " | 103.5 | " | + | ++ | 38 | 34 | 35 | 4 | 5 | 4 | 12000 | 14800 | 13000 | 51 | 69 | 52 | 42 | 19 | 40 | 0 | 11 | 3 | 7 | 1 | 5 |

TABLE IV.—RATE OF SEDIMENTATION AFTER ONE, TWO AND THREE HOURS BEFORE, DURING AND AFTER SPECIFIC STIMULATION.

TABLE IV.—RATE OF SEDIMENTATION AFTER ONE, TWO AND THREE HOURS BEFORE, DURING AND AFTER SPECIFIC STIMULATION.

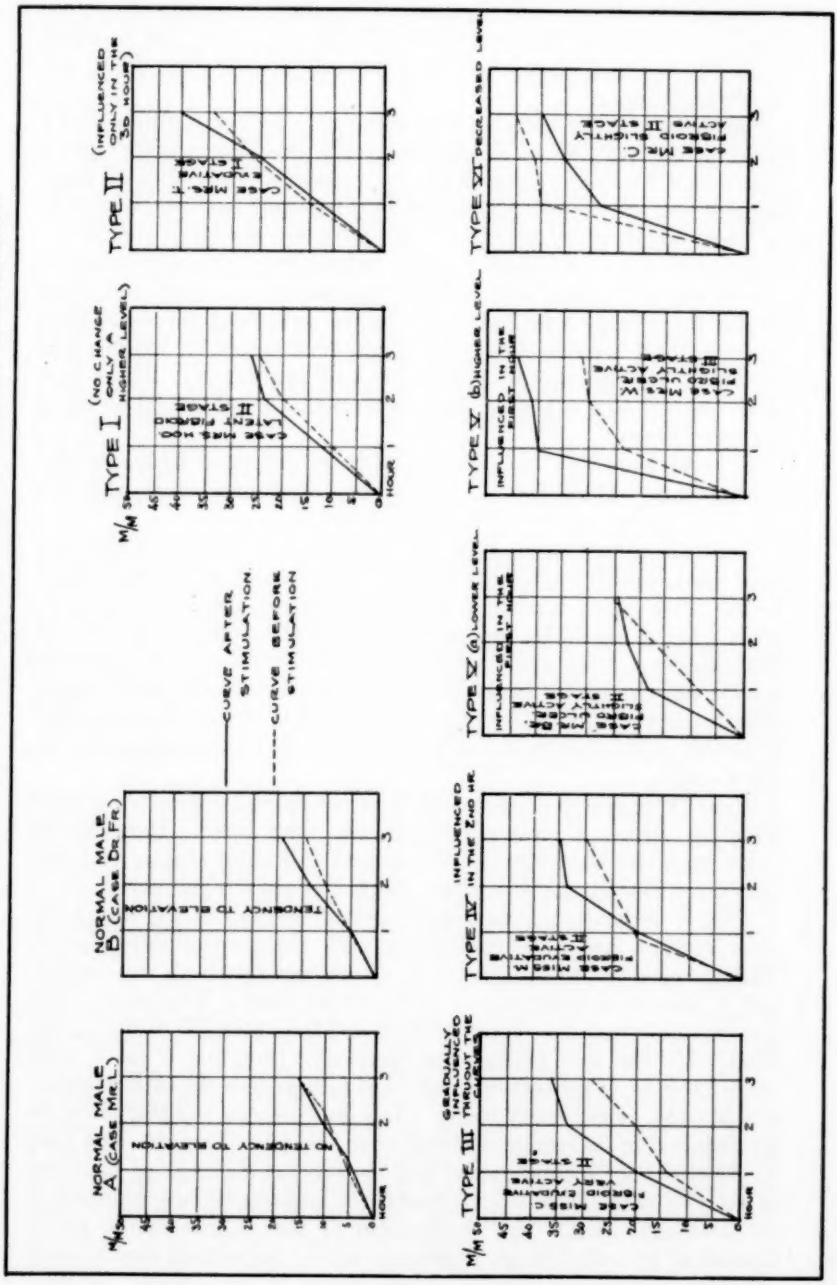
\+ INCREASED LEVEL AFTER STIMULATION
− DECREASED " " "
* HIGHER LEVEL WITHOUT STIMULATION
● DELAYED REACTION

| | 1 HOUR | | | 2 HOURS | | | 3 HOURS | | |
|---|---|---|---|---|---|---|---|---|---|
| | BEFORE STIMUL | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL | 24 HRS LATER | 72 HRS LATER |
| NAME | NORMAL CONTROLS | | | | | | | | |
| DR. S. | 2 | 3 | 2 | 4 | 6 | 4 | 12 | 15 | 13 |
| DR. FR. | 4 | 4 | 4 | 8 | 12 | 8 | 14 | 17 | 14 |
| MR. L. | 4 | 5 | 4 | 10 | 10 | 10 | 14 | 14 | 14 |
| MR. O. | 4 | 5 | 4 | 9 | 9 | 10 | 13 | 14 | 17 |
| MR. K. | 6 | 16+ | 6 | 14 | 26+ | 14 | 17 | 28 | 17 |
| | | I STAGE | | (CASES ON ADMISSION) | | | | | |
| MRS. F. | 15 | 12 | 15 | 21 | 20 | 21 | 27 | 33+ | 29 |
| MISS V. Z. | 7 | 7 | 8 | 12 | 15 | 18 | 20 | 20 | 23 |
| MR. B. | 15 | 14 | 15 | 22 | 22 | 23 | 22 | 27+ | 25 |
| MISS B. | 13 | 13 | 16● | 20 | 20 | 24 | 25 | 26 | 26 |
| MISS T. | 15 | 16 | 15 | 32* | 30 | 30 | 37 | 34 | 36 |
| | | II STAGE | | (CASES ON ADMISSION) | | | | | |
| MR. BR. | 8 | 17+ | 7 | 15 | 22+ | 16 | 25 | 25 | 25 |
| MRS. HO. | 18* | 18 | 18 | 26 | 26 | 25 | 29 | 29 | 30 |
| DR. W. | 20* | 32+ | 32 | 30* | 37 | 37 | 37 | 38 | 39 |
| MR. C. | 39* | 27− | 30 | 40 | 35− | 39 | 44 | 40 | 41 |
| MR. BI. | 3 | 5 | 2 | 7 | 8 | 6 | 13 | 15 | 11 |
| MISS M. | 22* | 20 | 23 | 26 | 32+ | 27 | 29 | 34+ | 31 |
| MR. G. | 21* | 29+ | 12 | 29* | 35+ | 19 | 31 | 35 | 29 |
| MRS. E. | 11 | 9 | 11 | 19 | 18 | 19 | 26 | 28 | 26 |
| MR. GR. | 34* | 28− | 30 | 39 | 36 | 36 | 40 | 40 | 36 |
| MRS. W. | | | | | | | | | |

| | 1 HOUR | | | 2 HOURS | | | 3 HOURS | | |
|---|---|---|---|---|---|---|---|---|---|
| | BEFORE STIMUL | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL | 24 HRS LATER | 72 HRS LATER | BEFORE STIMUL | 24 HRS LATER | 72 HRS LATER |
| NAME | NORMAL CONTROLS | | | | | | | | |
| DR. FL. | 12 | 11 | 11 | 17 | 15 | 15 | 20 | 19 | 20 |
| MISS K. | 11 | 13· | 11 | 21 | 21 | 21 | 29 | 25 | 29 |
| MISS G. | 11 | 13 | 11 | 16 | 19 | 16 | 21 | 22 | 21 |
| MISS D. | 8 | 9 | 8 | 20 | 18 | 20 | 23 | 20 | 23 |
| | | III STAGE | | (CASES ON ADMISSION) | | | | | |
| MRS. W. | 22* | 38+ | 38 | 29* | 40+ | 40* | 31* | 43+ | 43 |
| MRS. EA. | 30* | 36+ | 35 | 39* | 40 | 35 | 42* | 41 | 41 |
| MISS DR. | 29* | 35+ | 29 | 38* | 39 | 36 | 42* | 40 | 38 |
| DR. R. | 27* | 30 | 25 | 37* | 33 | 35 | 40* | 35 | 40 |
| | | I STAGE | | (CASES UNDER TREATMENT) | | | | | |
| MRS. BE. | 5 | 3 | 5 | 15 | 20+ | 12 | 19 | 29+ | 20 |
| | | II STAGE | | (CASES UNDER TREATMENT) | | | | | |
| MISS C. | 13 | 18+ | 10 | 20 | 34+ | 20 | 27 | 36+ | 26 |
| MRS. H. | 10 | 16+ | 10 | 18 | 25+ | 24 | 26 | 31+ | 27 |
| MISS SH. | 2 | 6 | 3 | 7 | 9 | 7 | 10 | 16+ | 12 |
| MR. MC. | 24* | 26 | 26 | 32 | 33 | 30 | 33 | 35 | 36 |
| | | III STAGE | | (CASES UNDER TREATMENT) | | | | | |
| MR. T. | 6 | 8 | 6 | 9 | 18+ | 24 | 15 | 25+ | 26● |
| MR. BEN. | 15 | 15 | 18 | 30* | 26− | 26 | 33* | 31 | 31 |
| MR. SK. | 22* | 27+ | 25 | 25 | 27+ | 32 | 33 | 35 | 34 |
| MR. V. | | | | | | | | | |
| MR. SU. | 4 | 9 | 5 | 22* | 15− | 15 | 26 | 19− | 30● |

This is the reason for the different and sometimes unfavorable criticisms which have been made against the value of it. Grafe and Rheinwein[1] desired to show relations between the activity of the cases and their sedimentation test. They injected patients with 0.03 to 0.3 mg. old tuberculin, and they claimed that a change of 3 mm. in the sedimentation twenty-seven hours after tuberculinization is indicative of activity. But this could not be confirmed on investigation (Brunecke,[5] Freund and Henschke[6]), probably because Grafe and Rheinwein have considered only readings in the first hour, and have paid more attention to the little observable changes of the height of the sedimentation than to the type of sedimentation curves. Fischel[7] attempted to establish this in his work, giving three types of curves, each of them being characteristic of a certain course of the disease. The first type resembles very much the type of the normal sedimentation, which has a tendency to be low in the first, and more accelerated in the second and third hours, only the values rise higher. The second type reaches its highest value in the second hour, being slightly above normal in the first, and only very slowly accelerated toward the third, sixth, and so forth, hours. The third type has an almost vertical ascending limb during the first hour, and has but little tendency to be accelerated later. The first type has a very good prognosis, the second rather favorable, and the third type a very bad prognosis, according to Fischel. Kersenboom[8] attempted to establish in the same way the types of sedimentation curves with finer gradations because he constructs his four-curve types by observing the speed of sedimentation in every ten minutes in the first hour, later in every thirty minutes. He claims that the sharper the angle of the curve the worse the prognosis. We could not compare our results with those of Kersenboom because we read our results during three hours, but as for the curves of Fischel we can say that we can generally confirm his results, except in certain cases. For instance, we had a patient on the borderline between the second and third stage with a lower sedimentation belonging more to the second type of Fischel, and we also have patients of the first stage with a higher sedimentation level who improved very rapidly, and observing their sedimentation curves we were compelled to put them, together with former cases, in the curve Type II, which classification, considering their rapid improvement and rather little anatomical defect could not be considered satisfactory. We attempted, as shown in Chart, by combining the method of the extract stimulation and the construction of the sedimentation curve to establish finer differences. Among our normal controls we could observe two types of the reaction in the sedimentation to extract doses. One type is not inclined to change its former level of sedimentation after extract doses in any of the hours; the other type shows a tendency beginning from the second hour, to be elevated,

CHART.—SEDIMENTATION CURVES BEFORE AND AFTER SPECIFIC STIMULATION.


NORMAL MALE
A (CASE MR. L.)
NO TENDENCY TO ELEVATION
NORMAL MALE
B (CASE DR. FR.)
TENDENCY TO ELEVATION
CURVE AFTER STIMULATION
CURVE BEFORE STIMULATION
TYPE I (NO CHANGE ONLY A HIGHER LEVEL)
CASE MRS. HOD. LATENT FIBROID STAGE
TYPE II (INFLUENCED ONLY IN THE 3d HOUR)
CASE MRS. T. EVOLUTIVE FIBROID STAGE
TYPE III GRADUALLY INFLUENCED THROUGHOUT THE HOUR
CASE MISS C. FIBROID EXHAUSTING VERY ACTIVE
H STAGE
TYPE IV INFLUENCED IN THE 2ND HR.
CASE MRS. S. FIBROID EVOLUTIVE ACTIVE
H STAGE
TYPE V (a) LOWER LEVEL INFLUENCED IN THE FIRST HOUR
CASE MRS. W. FIBROID SLIGHTLY ACTIVE
H STAGE
TYPE V (b) HIGHER LEVEL INFLUENCED IN THE FIRST HOUR
CASE MRS. W. FIBROID SLIGHTLY ACTIVE
H STAGE
TYPE VI DECREASED LEVEL
CASE MR. C. FIBROID SLIGHTLY ACTIVE II STAGE
M/M
HOUR

although very little (2 to 3 mm.). This slight tendency to elevation is perhaps due to the slight rise of temperature, but in other cases the sedimentation remains constant, despite the slight rise of temperature.

The first type of our curves corresponds to the normal, which have no tendency to be accelerated, only reaching a higher level. Changes of 2 to 3 mm. have not been considered, only above 5 mm., but this was not present. Some of our first-stage patients, who were in very good physical condition—afebrile, fibrotic, and those with tuberculosis of lymph glands—belong here, also a progressive case in the first stage, who later on was much improved, and those of the third stage who had been under treatment for some time and who had become desensitized and had gained in weight, and in whom the disease was inactive and stationary. These last cases have shown a higher sedimentation level (about 30 to 35 in the third hour).

Type II shows an acceleration only in the third hour, usually only 5 mm. Here belong the fibrotic and exudative and the rapidly improving cases of the first stage.

Type III represents curves the rise of which begins in the first hour, and slowly reaches its highest level in the second and third hour. This curve type is a more transitional one, because in its lower level it resembles the second type of the normal curve which has a tendency to be increased after extract injections; in its medium level it represents the exudative cases of the first and second stages, with good prognosis, and in its highest level it represents the rather favorable stationary cases, with a tendency to be progressive in the third stage.

Type IV shows an acceleration from the second hour after extract injection, which is most marked in the third hour. Here belong cases from the borderline of the second and third stages, and one exudative case of the first stage which was always subfebrile.

Type V represents a very high ascending limb in the first hour after extract injection, comparing with the unstimulated speed. This change, due to its sharpness, disappears slowly in the second, and is almost entirely absent in the third hour. This curve type has two subtypes, one (A) of a lower, and the other (B) of the higher level. To the first belong the ulcerative progressive cases with small cavities, of the second stage, and to the other the rather unfavorable cases of the third stage. *As a rule one can say that the more the influence of the extract is shifted from the third toward the first hour in the change of sedimentation, and the sharper the angle of the curve at the first hour the more unfavorable the immune-biologic behavior of the particular case.* The observation of the sedimentation curve instead of its speed alone, represents a very important step toward evaluating the finer changes in the course of the disease, yet this does not always give satisfactory results. The observations after

tuberculin stimulation alone also did not succeed in the differentiation of active and nonactive cases. It may be that the combination of both methods will be more successful. With few exceptions our cases belong to Types I and II of K. Fischel. The division into 4 to 5 types we believe to have given a further refinement, and these subdivisions aid especially the understanding of the borderline cases. Taking into consideration the small number of our cases we regard our subdivisions and the significance attached to them only as tentative.

In 3 cases we observed a marked decrease in the speed of the sedimentation after the administration of watery extract. The curve of the sedimentation was different in the different cases. In 2 cases there was present a very great increase of the skin sensitiveness, in the third a decrease connected with the retardation in the sedimentation, and in all 3 cases eosinophilia was present. The number of cases is too small to allow any conclusion as to whether or not there is a connection between these phenomena.

Concerning the value of sedimentation after the effect of the extract injection disappears, we can say as a rule that accelerated and retarded values both have an expressed tendency to return to the original levels, and in some cases remain stationary even when the clinical signs are much improved. Only in very few cases did we observe that the return to the original level was delayed. One of these cases (Case T.)—a progressive cavity case with tuberculous laryngitis—has shown almost normal levels (6 to 8 to 15). Only by tuberculin stimulation could we detect the real status of the patient by the increase of the sedimentation levels near to the pathologic range, and it remained at the same accelerated level several days after the extract injection. This level was not at all high (25 mm.), but serves to emphasize that delayed reaction, although not marked, has a certain significance. Also a patient of the first stage who did not respond well under specific treatment shows this delayed reaction (Case Miss Bo.).

Concerning the skin sensitiveness we have to make first a comparison between our normal controls and those of Tables II and III. As to the size of skin reaction we are not able to say that there is a real difference between the normal and tuberculous patients. In normal cases, the areas vary with the doses of extract used by us, as shown in Table I, from 3 to 20 mm., and this, with few exceptions, is also the extent of the reaction of the patients as shown in Tables I and II. With a certain generalization we can say that, looking over Tables I and II the area of the skin sensitiveness decreases when approaching the third stage, but this is not a rule, and small reactions (3 to 6 mm.) occur in normal controls as well as in the cases of the second stage. What we have said above regarding the behavior of the skin sensitiveness of normal controls not having the tendency to be influenced by the extract has more significance

because the opposite is observable in the skin sensitiveness of tuberculous cases. There is a change in a positive or negative direction in 17 cases out of 28. This change is present in the latent, stationary, and progressive cases, but has not much relation to the temperature because we did not observe its absence at normal temperature, and we can confirm the observation of Andrus, who also was not able to confirm the quite generally accepted opinion that the general reaction tends to induce lowered skin response. In our cases we can say that we have found that an opposite behavior is present; during a general reaction as a rule the skin sensitiveness is enlarged, although later it slowly decreases with the treatment. A certain connection with the sedimentation test is present, which, if it could be confirmed by further investigations would perhaps be a help toward the better understanding of the hypersensitiveness. It was claimed (Cardarelli[9]) that there is present some relation between the skin sensitiveness and lymphocyte count, elevated lymphocyte counts almost always running parallel with lowered skin sensitiveness, and conversely. In looking over Tables I and II we find a certain but not a constant connection between the skin sensitiveness and the lymphocytes, and we can say that the desensitization connected with the tuberculin treatment has not a close relation to the gradual elevation of the lymphocyte count following improvement in our cases.

Concerning the white blood picture we must first consider the whole white count. Formerly an increased white count was considered a sign of mixed infection, but now we have sufficient reason for the opinion that there can be an advanced pure tuberculosis with an increased white count. We quote here only the investigations of Schnorrenberg and Peters[10] who show that in cases in whose sputum there was found a mixed infection by bacteriologic cultivation on blood-agar that 63 per cent showed a leukocytosis of over 10,000, in those whose sputum remained sterile there was also found a leukocytosis in 48 per cent. This investigation is, however, not absolutely conclusive, because a mixed infection can be present even if we are unable to cultivate the microbes, yet it seems to us there are higher leukocyte counts in pure tuberculosis as well.

A neutrophilia more often indicates a mixed infection according to the same investigators, as a neutrophilia was present in only 4.9 per cent of the sterile, and in 37 per cent of the cases with mixed infection. Certainly this statement has no connection with the change of the blood picture after stimulation, because we have seen that our normal controls after extract doses react mostly with a slight rise in temperature, an increase in the whole white count and a neutrophilia.

Before we discuss our results concerning the blood picture we give here certain data from the literature, obtained after non-

specific stimulation. After the quartz-lamp treatment there is first a great decrease in the leukocytes, and after several hours one can observe a great hyperleukocytosis. First, there is a neutrophilia and lymphopenia, later lymphocytosis and eosinophilia (Constance, Nacke and Konigsfeld, Harrey[11]). The changes are similar after irradiation with visible rays. After a short leukocytosis (lasting one day) an increase in lymphocytes occurs, and there is then a slow return to the original level. (Sonne[12].) With nonspecific protein (1 per cent Yatren-caseosan) O. Seitler[13] got, according to the progress of the particular case, more or less increase in the neutrophiles and decrease in the lymphocytes, with or without increase in the whole white count.

Comparing the general effect of specific stimulation upon the white blood picture with the unspecific, we see that reading the blood picture within twenty-four hours after our extract stimulation we shall find with few exceptions the same tendency of the reaction—more or less a leukocytosis with neutrophilia and lymphopenia; the Arneth-Schilling formula being shifted to left. But we have also cases, although few, in which the tuberculous organism reacted with a lymphocytosis. So there is not present a definite response to our specific stimulation, but the analysis of the delicate changes in the blood picture may give us, as we will see later, very useful information.

Before the discussion of our own results we think it useful to give a short description of the observations of Romberg,[14] of Eicke,[15] and the conception of Schilling concerning the significance of the changes in the blood picture. Romberg classified tuberculous blood pictures in six classes, ranging from 0 to 5. Class 0 represents the blood picture of a very early case with no leukocytosis, no shifting to left with lymphocytosis with or without eosinophilia. This picture changes slowly with the appearance of the more or less pronounced leukocytosis, shifted Arneth formula, neutrophilia, disappearance of eosinophiles, and reversion of the lymphocytosis to normal in the Classes 1, 2, 3, 4a, 4b, and eventually may reach the very unfavorable picture of Class 5, with normal whole count, high neutrophilia, and lymphopenia. Romberg and his school have shown that by means of the tuberculin treatment one is able to demonstrate in the favorable cases the improvement of the blood picture from the medium favorable Class 3, 4 in the direction of class 1 or 0. It was he who on the basis of earlier investigations of Brosalem and Michels called the appearance of the eosinophiles in the blood picture the "dawn of the improvement," but he emphasized that the real improvement can only occur by the way of lymphocytosis.

Romberg has not considered in his scheme the monocytic system. Schilling in his book has proposed a classification according to the role of the three hemopoietic systems in the defense of the organism

against every infectious attack. According to his opinion one can speak of a "fighting phase," where the chief work is done by the neutrophiles, the number of which is in this phase much increased. With a growing defensive strength of the organism this phase is going into the "monocytic-defensive" phase. This is sometimes short-lived (two or three weeks) and is sometimes not discovered if blood examinations are not made at short intervals. If high monocytic count is connected with an expressed neutrophilia, this stage is very near the fighting phase, and it means that due to the great toxic overstimulation the organism is compelled to mobilize more and more monocytic cells from the extravascular tissue in order to take up and store particulate matter, probably cell débris, the residue of the fight between toxic agents and tissue cells. If a higher monocytic count is connected with an eosinophilia or lymphocytosis we can assume that the defensive strength of the organism has conquered the toxic effect of the bacillary invasion and is already approaching the third stage of Schilling, that of the *lymphocytic improving stage*. The greater the toxic offense, the oftener we shall see after its subdual, monocytosis connected with eosinophilia and lymphocytosis; the less the offense, the rarer is the appearance of the monocytes and the neutrophile fighting phase turns slowly, with or without eosinophilia, (sign of more or less hypersensitiveness) into the lymphocytic stage.

Schilling's classification is more or less applicable also to the course of tuberculosis. Certainly the more acute the form of tuberculosis, the oftener we see neutrophilic blood pictures connected with a strong shifting to left, and monocytosis. But as a rule, the ordinary blood picture that we see in the less active cases of the first and second stage is: Increased whole white count 10,000 to 12,000) with normal or decreased neutrophiles (50 to 60 per cent) and an increased or overnormal lymphocytosis, (30 to 40 per cent) with or without eosinophilia. The Arneth-Schilling formula is almost always more or less shifted, very seldom normal, mostly over 7 per cent.

The blood picture would correspond to the so-called lymphocytic improving stage. The tuberculous organism, due to the chronic character of the infection and to the self-immunizing effect of the tuberculous foci, creates a labile balance between offense and defense, and the sign of it is the lymphocytosis, with more or less shifted neutrophile formula. If other chronic diseases can be excluded this blood picture may sometimes serve as a very important diagnostical aid in conjunction with physical examination. The importance of the blood picture is enhanced because in early tuberculosis the sedimentation, complement-fixation, and flocculation tests are unreliable. By means of specific stimulation we can receive further information. Reading the blood picture before, during, and after specific stimulation as shown in Tables II and III we are able first to detect the relation between offense and defense, which is sometimes marked by the natural labile balance, as above mentioned

and further, we can control the specific therapy, measuring the effect of our doses by the promptness of the return or delay of the stimulated level to the original reading. Generally one can say that every stimulation puts back the blood picture in a less favorable stage than it was before the stimulation. Eicke calls this reaction a negative phase. If after seventy-four hours the return to the original reading is prompt, or if the blood picture sometimes shows an improvement in the sense of Romberg or Schilling, Eicke speaks of a positive phase, which means that the selected doses were correct, and the hemopoietic system is in a condition to respond to specific treatment without overstimulation. If the return is not prompt, but delayed, we can conclude either that the selected dose was an overstimulating one or that the form of the disease is that of a slowly reacting one. On repeating the dose or giving a smaller one we can decide which assumption may be considered correct. If the repeated doses cause the same delay, and the use of a smaller dose causes a prompt return to the original level, there was an overstimulation; if with the smaller doses the same delayed reaction occurs we have a slow-reacting form of the disease before us.

Sometimes there is only a reaction in the Arneth-Schilling formula, the other parts of the blood picture remaining unchanged. This occurs in the far-advanced cases, and, although not sufficiently studied, and is in our opinion rather an unfavorable sign. (Case Dr. R., who died later, and Mrs. W., a third-stage cavity case.) Conversely, if the Arneth-Schilling formula is not influenced by the specific stimulation—it is immaterial whether or not there is a change in the other part of the white blood cell picture—it is a very favorable sign. The cases belonging to this type have the best prognosis. The only difference in these cases in comparison with the normal controls is that the Arneth-Schilling formula runs on a higher level. (Cases Mr. Sk., Mrs. E. A., Table III, Miss Be., Miss V. Z., Table II.) Sometimes, only in few cases, and those only of the most improved type, the Arneth-Schilling formula shows normal readings. (Mrs. H. and Mr. Su., Tables II and III.) This is very rare, because on the other hand cases with healed hilum tuberculosis with almost no physical symptoms show a change after extract stimulation in their neutrophile formula as a sign of the past disease (Case Sh., Table III).

Our observations on the whole confirm almost exactly the observation of De Pace,[16] who described three types of blood reaction following tuberculin treatment: *The early reaction*, the blood reacting even after two to three injections, in the ordinary way with leukocytosis, neutrophilia, and decrease of lymphocytes; *the delayed reaction*, in cases having leukocytosis, and reacting from the third week mostly to higher doses, and finally *the reaction of the anergetics*, where the stimulation remains unsuccessful.

Judging the neutrophile formula as a sign of an active infection we must emphasize that this has only value by excluding other

infection, because simple colds, bronchitis, and so forth, have an elevating effect upon it.

To establish a nearer relation between quantitative stimulation and the qualitative response of the organism represented by the histologic blood picture we must observe patients in different stages of the disease and stimulate them with different doses. The rhythm of the stimulated blood picture must be followed from the beginning of the supposed reaction, and as far as possible. Not considering the return or delay of the histologic blood reaction after certain days, earlier investigators believed a neutrophile reaction after certain days indicated a good prognosis (Brodin and Giron,[17] Roth). This is, as shown, only a half truth, not the stimulated level alone is important, but also the return or delay after several days to the original level. Eicke follows the blood picture five to six days after the stimulation, but he does not begin sufficiently early with his observations. Even Brosalem[18] mentions that one hour after specific stimulation by medium-sized doses there is an eosinophilia at times when the whole white count and the neutrophiles are not changed. In a few of our cases we tried to follow the whole rhythm of the stimulated blood picture, starting from one hour after the stimulation and continuing for four days, and making twice daily—forenoon and afternoon—an examination to observe the eventual change caused by the daily rhythm of the white blood picture, lately studied by Sabin[19] and coworkers, and comparing our cases with observations on normal persons through several days after specific stimulation. These cases are too few to enable us to draw further conclusions, but they confirmed the observation that there is an eosinophilia present one hour after the specific stimulation, and a daily rhythm was also observed.

We consider our work as preliminary to one in which all the above-mentioned qualitative and quantitative refinements shall be considered. We said at the beginning that at this time we look upon tuberculin more or less as a substance with which we stimulate the tuberculous organism to certain reactions, similar to those which were received by unspecific stimulation. But we are of the opinion that the specific stimulation may have a deeper relation to the reactions of the tuberculous organism than has the nonspecific, and this applies especially to hypersensitiveness, and following more closely the rhythm of the change in the white blood picture, perhaps even by these specific reactions a more definite response to the specific stimulation can be detected.

**Summary and Conclusions.** The effect of specific stimulation on the rate of sedimentation, skin-sensitiveness, and the leukocyte picture was studied in the case of 28 patients on admission, and after treatment. Our results appear to be as follows:

1. The sedimentation test is more sensitive to the specific stimulation than is the focal reaction, and is more adaptable in establishing certain rules concerning the reactions of the organism than is the

skin sensitiveness, due to its greater independence of constitutional factors. The sedimentation test is as sensitive as the temperature. The differential white blood picture is more sensitive to specific stimulation than the temperature and the sedimentation test.

2. We can confirm the opinion of K. Fischel that the curve of sedimentation has more significance than the rate. Combining the construction of sedimentation curves with the effect of specific stimulation five types of the reaction are tentatively given which would express the progressing activity of the disease.

3. The skin sensitiveness of normal controls is variable, but has no tendency to be influenced by specific stimulation. The skin sensitiveness of patients varies in the same way, but can be influenced by specific stimulation, especially at the beginning of the treatment. The connection of the decreased skin-sensitiveness to lymphocytosis and to the shifting to left in the neutrophile formula can be seen in only a few of our cases.

4. By specific stimulation the majority of our cases reacted with a neutrophilia, and with a decreased lymphocyte count. The promptness or the delay of the return of this stimulated level after two to three days to the original reading, or a change into a worse or an improved blood picture gives us valuable information in regard to the type and severity of the reaction, and serves as a guide in measuring our doses. Delayed reactions, seventy-four hours after stimulation, indicate either the slowly reacting form of the disease or a response to overstimulation. Only a few cases react to specific stimulation with a lymphocytosis. Whether this is a sign of a great natural resistance at the beginning of the treatment, or of a great improvement following the treatment, or only of a desensitization after prolonged treatment, cannot be determined.

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# SPIROCHETAL JAUNDICE IN THE UNITED STATES.

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There is still uncertainty regarding the etiology of infectious jaundice. It may well be that in different instances and in different localities very different causes are operative. In some cases undoubtedly the Leptospira icterohemorrhagiæ is the causative agent, but in this country proved cases of infection by this organism are very few. Additional data and records are urgently needed, for the question whether the condition is being overlooked or is actually rare in the United States is an important one.

Epidemics of jaundice, however, are by no means infrequent in this country, and have been known in Europe from the earliest times. Cockayne[1] gives a full historical bibliography. A distinct contribution to the nosography of jaundice was made by Weil[2] who in 1886 described 4 peculiar cases of jaundice associated with splenic enlargement and nephritis, and called attention to the relapses of fever that occurred in 2 of the cases. Since this publication the occurrence of fever, jaundice and subcutaneous hemorrhages, albumin and casts in the urine, has frequently been called Weil's disease.

A disease very similar to that described by Weil is prevalent in Japan, and in 1914 Inado and Ido[3] discovered a spirochete in the blood and tissues of patients suffering from this condition. The name Leptospira icterohemorrhagiæ was later (1917) suggested for the organism by Noguchi[4] because of certain distinctive characteristics. Similar or identical organisms were subsequently recovered from cases of jaundice in Germany,[5] France,[6] Italy,[7] Scandinavia[8] and England.[9]

This led to the belief that the leptospira might be the common cause of infectious jaundice, but Witt,[10] Wadsworth,[11] and Williams[12] failed to find it in cases of infectious jaundice in this country, and Blumer,[13] from an analysis of epidemics of jaundice in the United States since 1812, coupled with his failure to find the leptospira even by modern methods, concluded that this organism was not the cause of the common, non-fatal form of epidemic or infectious jaundice in this country.

**Symptomatology.** The onset of Weil's disease is usually sudden, with headache, injection of the conjunctiva, extreme prostration,

and pains behind the eyes and in the legs. Gwyn[14] lays great stress on the muscle pains, regarding them as possibly due to a myositis resulting from the presence of the parasites in the muscle. Herpes is common. The temperature is elevated to 100° to 103° F., the pulse rapid. Jaundice appears about the fourth day and gradually deepens until the eighth or ninth day. Jaundice may, however, be absent.[15] The liver is usually enlarged and tender. Although splenic enlargement was noted by Weil, the spleen has not been demonstrably enlarged in the majority of cases. It was noted in only 2 cases in Dawson's series, and in but 10 per cent of the cases studied by Inado and his associates. Subcutaneous and submucous hemorrhages occur in many of the severe cases. The urine is constantly reduced in amount and contains albumin, casts, and bile. There is usually a leukocytosis, in some cases as high as 25,000. In uncomplicated cases the patient begins to improve, and the jaundice to disappear, at the end of the second week. There is frequently a second elevation of temperature during convalescence, as noted by Weil. This occurred in 40 per cent of the European cases according to Fiedler,[16] and in 28.2 per cent in Inado's series.[16] Convalescence is established between the third and fourth week. In fatal cases, death usually occurs about the end of the first week. The mortality is much higher in Japan (38 per cent) than in Europe (estimated at 2 to 5 per cent). Noguchi suggests that this may be due to an increase in virulence of the Japanese strain owing to a more frequent passage through man.

The opportunities for postmortem examination have been few. The usual changes, as described by Dawson[15] and Stokes[6] consisted in lesions in the intestinal tract, liver and kidneys. The mucosa of the duodenum was swollen and bluish-red in color. The lower part of the common bile duct within the duodenal wall shared in this inflammation, producing biliary obstruction. Scattered subperitoneal hemorrhages were commonly found over the small intestine. The liver was bile stained, and in sections showed collections of small mononuclear and polynuclear cells in the portal areas, and toward the centers of the lobules both intracellular and extracellular granules and masses of pigment. Stokes in 2 cases described an exudation of cells into the interstitial tissue surrounding the smaller bile ducts. In the kidneys the glomeruli showed no changes while the tubules presented swelling and granular degeneration of their epithelium, polymorphonuclear exudates between the tubules, and hemorrhages into their lumen in poorly defined patches. The lungs usually show hemorrhages of varying size.

The leptospira may occasionally be demonstrated in the blood during the first few days by dark-field examination. The diagnosis is more frequently made by injecting blood or urine into a guinea pig. This animal is very susceptible, developing after six to thir-

teen days a fatal infection characterized by jaundice, hemorrhages, and pyrexia. With the onset of the pyrexia, leptospira can be demonstrated in the urine, and postmortem in the tissues of the animal.

**Treatment.** The Japanese workers in their first paper pointed out that the blood of convalescent patients contained substances that would protect a guinea pig against infection, and that were also capable of curing the disease in the guinea pig if injected before the development of jaundice. On this basis, both the Japanese and French have prepared an antiserum which has given very promising results in several cases.

Treatment is only difficult in the severe cases, and here the curative serum alone offers an effective remedy. Arsphenamin has been tried, but is without benefit.

The leptospira is a common parasite of apparently healthy rats in many parts of the world, and has been found in this country in rats caught in various parts of New York State,[4,11,17] Baltimore[18] and Nashville.[19] Direct infection from rat bite, while it may occur, is apparently uncommon. The rat acts as a carrier of the organism, infecting soil and water with its urine, in which the leptospira are eliminated. Guinea pigs may be infected by feeding cultures, or by the penetration of the organism through the unbroken skin.[3] There is evidence that man may also be infected by either of these routes. Moreover, leptospira have been found in tap water in London,[20] in the Thames and in water in the Lothian mines. So far as we know they have not as yet been demonstrated in water supplies in this country. Wolbach and Burger in 1914 cultivated a free living, filterable spirochete from the waters of a Boston pond. They believed it to be a new species (S. elusa). Its pathogenicity was not determined.[21] The presence of leptospira in water is of importance, for Zuelzer[22] has shown that nonpathogenic water leptospira may acquire pathogenic properties after long culture, and Buchanan[23] produced fatal jaundice in guinea pigs by injecting slime containing spirochetes. The viability of leptospira in soil and water seems to depend upon the reaction, cases being more frequent in parts of Japan where soil and water are alkaline.[24]

Although reports of isolated cases and small epidemics of "Weil's disease" are not rare in the American literature of the past few years, we have been able to find only 4 cases in which the leptospira was demonstrated.

The first of these was reported in 1922 by Wadsworth[11] in a laboratory worker.

While preparing to inoculate a rabbit, one of the laboratory workers pricked her finger with the needle of a syringe containing a culture of leptospira obtained from a rat. Seven days later she developed fever, general malaise, nausea and vomiting. Fever lasted for ten days. There were no signs of involvement of any

of the organs, no bile or casts in the urine, and no significant albuminuria. There was no jaundice beyond a possible brief tinging of the sclera. There was a moderate leukocytosis. Leptospira were demonstrated in the tissues of a guinea pig which had been inoculated with blood drawn on the fourth day of the disease.

The second case was reported by McDowell[17] in January 1925.

A man, aged forty-three years, who worked and slept in a kitchen infested with rats, suddenly developed a temperature of 103° F. and pains in his joints, back and abdomen. Three days later he developed a total anuria. He became deeply jaundiced, vomited bloody material and passed blood by bowel. He died one week after the onset of his illness. A drachm of urine obtained by catheter contained albumen, casts, bile, and red and white blood cells. His blood Wassermann was negative. Postmortem examination showed no evidence of liver atrophy. There were petechial hemorrhages throughout the intestinal tract. The kidneys were large and swollen, showing an acute glomerular nephritis on section. Leptospira were demonstrated in sections of the liver and kidneys.

Although infection here may well have been from a rat bite, the case is clinically one of spirochetal jaundice, and not one of rat-bite fever. Rat-bite fever is caused by another parasite, the Spirocheta morsus muris, and is characterized by swelling of the regional lymph glands, repeated paroxysms of fever lasting a few days, and a characteristic rash. The renal lesions in this case differed from those usually found in the degree of glomerular damage.

The other 2 cases were recently reported from Philadelphia by Sailer:[25]

Case I.—A white man, aged fifty-one years, had been sick nine days with chills, fever and pains all over his body. Jaundice had appeared early and become steadily deeper. Liver and spleen were not perceptibly enlarged. The calf muscles were exquisitely tender. Urine contained albumen and bile. Blood Wassermann test was negative. Spirochetes were seen in the blood by dark-field examination on the tenth day of the disease. Convalescence was uneventful.

No guinea pigs were inoculated with material from this case, nor were the leptospira demonstrated in permanent preparations. The organisms usually disappear from the periperal blood by the seventh day, so that their presence in dark-field preparations on the tenth day is of considerable interest.

Case II.—A man, aged forty-four years, was stricken with headache and general stiffness one week after being drenched in the rain. The following three days he suffered from vomiting and epistaxis, and was told that he was yellow. On admission to the Philadelphia General Hospital, his lips, ears and fingers were cyanosed, skin and sclera yellow and injected. Throat, heart and lungs were normal

Liver palpable 3 cm. below the costal margin. Urine contained a trace of albumin, a few red blood cells and bile pigment. There was no leukocytosis. Van den Bergh test was positive for obstructive jaundice. Urine, obtained on the eighth day of the disease, was injected into a guinea pig, and the leptospira demonstrated by Dr. J. C. Small in the animal's urine and tissues (kidney and liver). The patient improved rapidly and was discharged one week after admission.

The following case, then, is the fifth to be reported up to this time (December 20) in this country, and the third to be recognized in the vicinity of Philadelphia.

**Case Report.** L. K., a Russian laborer, aged forty-two years, was admitted to this hospital under the care of Dr. Stengel on October 14, 1925. Four days before (October 10) he had complained of chilliness, fever, and difficulty in swallowing. During these four days he had remained in bed at his home. On the second day he developed headache, and pains "all over his body," together with muscular soreness "as if someone had hit him," worse on attempts to move. He had no appetite, and vomited on several occasions after taking food. The day of admission to the hospital he had begun to cough, raising a yellowish, tenacious sputum. His past medical and family histories were entirely negative. He had been working in a building excavation on the outskirts of the city.

On admission to the ward, his temperature was 98° F., pulse, 112 and respirations 32 per minute. Blood pressure 90 systolic, 58 diastolic. He was obviously quite ill. On the first examination by artificial light, no jaundice was noted. His tongue was coated and there was a mild pyorrhea. The pharynx was moderately injected and showed a small amount of mucopurulent secretion. The examination of the head, lungs and heart disclosed no abnormalities. The liver was enlarged, extending from the fifth interspace to 2 cm. below the costal margin. The spleen was not palpable. A few inguinal lymph glands were enlarged, but none could be felt in the axillæ. His calf muscles were distinctly tender. The next morning, by daylight, he was definitely jaundiced.

*Laboratory Studies.* Erythrocytes, 4,400,000; hemoglobin (Haden-Sahli), 80 per cent; leukocytes 10,300; with 86 per cent neutrophiles, 12 per cent lymphocytes, and 2 per cent mononuclear cells. Urine acid, specific gravity 1.020, contained a cloud of albumin with many hyaline and granular casts, a few leukocytes, but no red blood cells. Blood Wassermann test was negative. Blood-urea nitrogen 67 mg. per 100 cc. Van den Bergh test: direct reaction immediate biphasic, indirect reaction 18.8 units.

*Course.* The morning after admission the jaundice was definite, the liver slightly larger and tender on palpation. Spirochetal jaundice was considered and leptospira were demonstrated by Dr. Lynch

in the blood by dark-field examination, and subsequently in the tissues of guinea pigs which had been inoculated with the patient's blood, as described below.

On October 16, the jaundice was much deeper, the liver larger and more tender. The patient began to hiccough, and vomited quantities of coffee-ground material which gave strong reactions for occult blood. Herpes labialis was noted. Stools contained bile pigment and macroscopic blood. The following day brought no appreciable change in his condition. On October 18 he was decidedly worse: jaundice intense, liver reaching 5 cm. below the costal margin. He had showers of subcrepitant rales at both bases. Blood-urea nitrogen 73 mg. per 100 cc., Van den Bergh test, indirect reaction 40+ units.

The patient died the evening of October 18, four days after admission to the hospital, and eight days after the beginning of symptoms. His temperature had risen to 102° F. three hours after admission, but fell to normal again by the following morning, and stayed below 99° F. Pulse rate ranged from 108 to 120. No postmortem examination was permitted.

Dark-field examination of the patient's blood on the sixth day of the disease, October 15, 1925, showed spirochetes.

Ten cubic centimeters of blood were taken directly into a tube containing 1 cc. of a 10 per cent solution of sodium citrate and allowed to settle for a half hour at room temperature. A drop of the supernatant serum was then examined by dark field and a number of actively motile organisms of the leptospira type were found.

Blood films were prepared on the same day and stained by various methods. In a film stained by Giemsa stain the organism shown in the accompanying photomicrograph was found. The film was fixed with methyl alcohol fifteen minutes and allowed to dry. It was then flooded with a freshly prepared solution of 10 drops of Giemsa stain in 15 cc. of distilled water. The slide was now warmed to steaming for fifteen minutes and allowed to stain cold for ten minutes longer, then flooded with distilled water, dried without heat and mounted.

*Animal Inoculations.* Three guinea pigs were inoculated on the seventh day of the disease with citrated blood.

Pig No. 1 received 0.5 cc. of citrated blood intraperitoneally. Pig No. 2 received 0.3 cc. intracranially. Pig No. 3 received 0.3 cc. intrahepatically.

All three pigs were found dead in their cages, one on the morning of the ninth day after inoculation and the others on the tenth day, all three pigs having progressively lost from 20 to 25 per cent weight, but appearing otherwise perfectly well up to the time of death. The pig inoculated intrahepatically died a day earlier than those injected intracranially and intraperitoneally.

*Guinea Pig Autopsies.* External appearance: There were no discharges from nose or mouth and no evidence of diarrhea. Jaundice was marked in the sclera and in the mucous membranes of the nose and mouth, and in all the light-colored areas of the skin. The animals did not appear markedly emaciated. The autopsy findings were so similar in all three animals that they can be given together.

Subcutaneous fat: Yellow.

Lymph nodes: Slight to moderate axillary and inguinal adenopathy.

Lungs: Petechial and gross hemorrhages and congestion.

Heart: No change.

Liver: Slight enlargement, with a greenish-yellow tinge and pig No. 1 had an area of necrosis along the edge of the liver. Pig No. 2 had a slight enlargement with marked yellow staining. Pig No. 3 had congestion but no yellow staining.

Gall bladder: Empty.

Stomach: One stomach normal, one ruptured and one distended, with petechial hemorrhages in the latter.

Kidneys: Enlargement, congestion and petechial hemorrhage. Pig No. 1 showed pale yellow tinge.

Spleen: No jaundice evident.

Bladder: Distended with thick mucinous urine.

Generative organs: The epididymi were markedly congested and the testes normal. The uterus was congested and the cavity filled with blood. There was an early right cornual pregnancy but the degree of congestion was unusual.

Intestines: No abnormalities except in pig No. 3 in which the colon was congested, and contained some blood in the lumen.

Adrenal: Congestion in pig No. 2.

*Microscopical:* Lymph nodes: Acute lymphadenitis in the enlarged nodes.

Lung: Acute hemorrhagic pneumonitis. Acute purulent bronchitis. Condition very similar with some variations in degree of involvement.

Liver: Cloudy swelling, most severe in No. 2. Fatty degenera-

tion and fat infiltration. Bile ducts plugged with bile stained mucus or inspissated bile.

Kidney: All animals showed very severe acute parenchymatous nephritis, with extreme congestion in the glomeruli and necrobiosis in the tubules.

Spleen: Slight or no acute splenitis in No. 1. Moderate acute splenitis in No. 2. Severe acute splenitis in No. 3.

Generative organs: Acute hemorrhagic epididymitis in pigs No. 1 and 2.

Levaditi: In sections stained by the Levaditi method spirochetes were found in the kidneys of all animals; in the lung of No. 1, and a few in the adrenals of No. 1, and a few in the livers of Nos. 1 and 2.

At the time of autopsy, heart's blood was taken from all three pigs and urine from pigs Nos. 1 and 2. Five other guinea pigs were inoculated with this material, but none of them became sick, and at autopsy some months later, when they had died from some intercurrent infection, none showed any pathology referable to the kidneys or liver, and although two of them died of pneumonia it was not similar to the pneumonitis in the first three animals.

**Comment.** The history, onset and physical findings in this case are quite typical of the disease. The concentration of bile pigment in the blood plasma, as expressed by the indirect Van den Bergh reaction is unusually high (20+ mg. per 100 cc.) and raises the question whether the jaundice is a purely obstructive one. The demonstration of the leptospira in the peripheral blood, both by dark examination and in fixed smears, and in the tissues of the inoculated guinea pigs definitely establishes the diagnosis.

In examining the blood by dark field, care must be taken not to mistake for spirochetes the very similar protoplasmic prolongations derived from crenating blood cells and from platelets. These bodies have been referred to previously by different observers and have undoubtedly been repeatedly mistaken for living bodies, particularly spirochetes. It requires some experience in dark-field examination of blood to identify them as pseudospirochetes, and a word as to their appearance might not be amiss. They are, as a rule, more coarse than spirochetes, and often have a small refractile knob at one end, giving somewhat the appearance of a sporulating tetanus bacillus. They do not possess true motility, as do spirochetes, but are so sinuous that as they float with the current in the preparation they give the appearance of actual individual motion. This may be so real in its appearance as to easily confuse one seeing it for the first time. There has never been a satisfactory explanation of their nature, and further studies are in progress at this clinic.

Attention should be called also to the appearance of the organism

in sections of tissue stained by Levaditi's method. They do not have, in tissue preparations, the delicacy they have in blood and are much more irregular in shape and size. Some of these shapes are quite bizarre and may readily be overlooked unless this pleomorphism, a good idea of which can be had by referring to Ido, Inado, *et al* (No. 3), is kept in mind.

**Conclusions.** Weil's disease is of sufficiently frequent occurrence to warrant the consideration of that diagnosis in any illness of sudden onset with headache, generalized pains, a sense of utter exhaustion, vomiting, conjunctival congestion, herpes labialis, a temperature up to 103° or 104° F. and jaundice appearing on the third or fourth day. A positive diagnosis requires the demonstration of the Leptospira icterohemorrhagiæ in the blood and urine, preferably by guinea-pig inoculation. The organism is not present in the blood as a rule after the seventh day.

It is very difficult to demonstrate the organism in the urine except by guinea-pig inoculation, as the urine is usually too cloudy to permit of satisfactory dark-field examination, and cannot, as a rule, be stained satisfactorily.

Special care should be taken to avoid the pseudospirochetes in the dark-field preparations and to allow for the pleomorphism of the organism in sections of tissue.

Because of the uncertainty of the incidence of infection by the Leptospira icterohemorrhagiæ in this country, it is extremely desirable that an unusual effort be made to demonstrate the organism in these cases.

Aside from the use of convalescent serum or the artificially produced antiserum, the treatment is entirely symptomatic.

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## A DEVICE TO GAUGE THE DEGREE OF SENSITIVENESS IN SUBNORMAL, NORMAL AND HYPERSENSITIVE AREAS.

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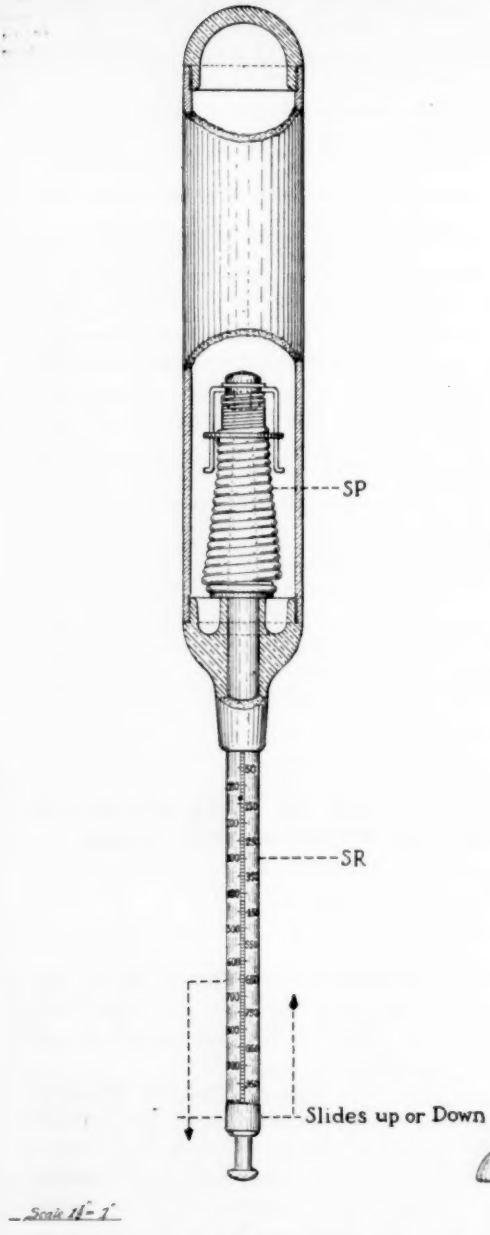
The need of an instrument capable of recording relatively the amount of pain a person experiences in various anesthetic and hyperesthetic areas, affected by disease, has prompted me to contrive this device, which I am about to describe.

This device, which I termed the "sensimeter," tends to eliminate to a great extent the patient's vague statement as to the amount of pain experienced, and enables the physician to gauge the relative amount of pain a patient suffers in a given location, as compared with the normal side. This method offers a more efficient means of recording the extent of injury, the progress of the condition, as well as the efficacy of the therapeutic agent employed.

The principle of this device is based on the maximum amount of pressure, measured in grams, a given area can withstand until sensation of pain or discomfort is complained of. It is quite obvious that sensitive areas will withstand less pressure than normal ones, while areas which are anesthetic or hypoesthetic will tolerate much greater



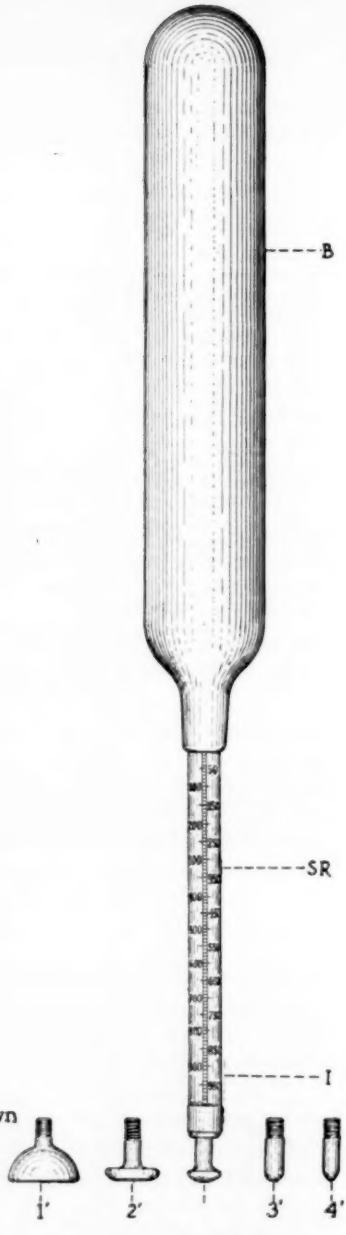




FIG. 1. FIG. 2.

FIG. 1.—Diagrammatic drawing showing inside structure of instrument. *SP* represents the spring in its position before the instrument is used. *SR* represents the sliding rod and scale. When pressure is applied downwards on the barrel, the sliding rod rises upward, carrying the spring with it. The latter is so constructed as to offer increased resistance with increased pressure, both measured in units of grams as registered on the scale. The maximum pressure it can register is 1000 gm.

FIG. 2.—Shows the external appearance of the instrument. When pressure is exerted upon the barrel (*B*), the latter slides down over the sliding rod (*SR*), pushing the indicator (*I*) in front of it. When the pressure is removed, the barrel returns to its original position, the indicator, however, remaining at the point where the maximum pressure has registered on the scale. In this manner the reading in grams of pressure is obtained from the scale.

1′, 2′, 3′, and 4′ are the different size detectors, which are used as required. The latter are screwed into the distal end of the sliding rod.

pressure. The amount of pressure required to produce pain will also depend upon the size of "detector" used (Fig. 2). The latter are four in number, varying from ¼ mm. to 7 mm. in width at the base. The wider the base of the detector, the more pressure does it require to produce pain. In this manner, any one of the detectors may be chosen, depending upon the areas to be tested, and the type of patient responding to pain.

The *modus operandi* is quite simple. The instrument is held at a right angle to the surface and pressure is exerted upon it slowly and uniformly, until patient complains of pain, at this point the pressure is removed and the reading obtained on the scale (Fig. 2), as shown by the indicator (Fig. 2, I).

The conditions in which this instrument proves to be of great advantage, are various forms of neuritis, neuralgias, myositis, arthritis, various neurologic diseases, eye diseases, such as glaucoma, suspicious cases of mastoiditis, where the diminution or increase in sensitiveness over the involved area is an important factor in prognosis and treatment. It also finds its use as a corroborative factor in inflammations of the nasal accessory sinuses.

This instrument is to be manufactured by Fred Haslam & Co., Brooklyn, N. Y., and may then be procured from any local surgical instrument dealer.

## ROENTGEN RAY STIMULATING DOSES OF THE OVARIES, PERMANENT AND TEMPORARY STERILIZATION.

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The term "stimulating" dose of Roentgen rays owes its existence to the biological law of Arndt-Schultz, which states that small doses of an agent stimulate, large doses paralyze cells. Careful investigations, undertaken recently seem to prove, however, that his law cannot be applied in general to Roentgen rays and although we would by no means state that the question is finally decided, it is preferable to speak, not of stimulating doses but of small doses of Roentgen rays, a term that presupposes nothing.

In gynecology, a number of conditions have been treated with a series of small doses of Roentgen rays directed to the ovaries; this is a group which might be classified as "Ovarian Dysfunctions." I am referring to disturbances of menstruation in young women, viz.: menorrhagia, dysmenorrhea, oligomenorrhea, and amenorrhea. These sometimes defy any therapeutic effort but, without doubt, respond to some extent to repeated small doses of Roentgen rays.*

* Hirsh, S.: Roentgen Therapy in Hypofunction of the Ovary. Read before the Annual Meeting of the Radiological Society of North America, Cleveland, O., December, 1925.

It is assumed that they either stimulate the ovaries or balance an abnormal function, but the exact mechanism of the effect is not known.*

Another group of patients presents an entirely different problem; in order to improve their condition a socalled "temporary" sterilization is to be considered. We take from the literature that this includes, for instance, women who have gone through a series of pregnancies with almost no interval for reasonable recovery, or married patients suffering from an acute disease which is usually followed by a long period of convalescence. Sometimes mild forms of pulmonary tuberculosis, not serious enough to demand a permanent sterilization, extreme forms of metrorrhagia or fibroids in young women, and pelvic inflammatory disease may be considered in this group.

It is known that a well-defined amount of Roentgen ray energy, very often called "castration dose," applied to the ovaries will cause permanent amenorrhea followed by all the symptoms of the climacteric. Early in the Roentgen therapy era, Gauss[1] suggested administering only part of the castration dose in order to cause the above-mentioned temporary sterilization. This has been tried out and a temporary amenorrhea was observed with a duration of from several months to three years. No exact data can be given as to the length of the amenorrhea in relation to the applied dose. The age of the patient is undoubtedly of importance (Kadisch[2]). Again, we can state that a considerable number of cases coming under this group have been treated and benefited. (Behrendt,[3] Weigand.[4]) As to the method of choice, it must be said that Roentgen ray and radium are identical in their effect. Matthews[5] and Kupferberg[6] prefer radium on account of a more accurate dosage. The disadvantage is that the patient has to be admitted to a hospital for the radium application.

Since the inauguration of Roentgen ray treatments in small doses for ovarian dysfunctions or with the aim of temporary sterilization, the question of an injurious effect on a future pregnancy has been widely discussed. There are only two ways to solve this problem; one is by the observation of women who have received either type of treatment mentioned, and the examination of children born later, the other is by carrying out animal experiments on a large scale to investigate probable changes in several succeeding generations. Against the latter method, the objection can always be raised that it is not permissible to transfer conclusions drawn from animal experiments to human beings. Both methods have been carried out, and studying the literature, one can easily find three different viewpoints as to the advisability of administering small

* A monograph has been recently published by F. C. Geller (Die Ergebnisse der experimentellen Eierstockbestrahlung, Ergebn. d. med. Strahlenforschung., Leipzig, 1926, **2**, 401).

doses of Roentgen rays to the ovaries of young women or attempting the temporary Roentgen ray sterilization.

The first group of authors, (Behrendt,[3] Weigand,[4] Nuernberger,[7] Pemberton,[8] Meiner,[9]), recommends both procedures and considers either of them harmless to future pregnancies; they emphasize, however, that it is very dangerous to treat during the term of pregnancy. Aschenheim[10] reports the birth of a microcephalic infant with bilateral microphthalmia to a woman who was treated twice for myoma during the first four months of pregnancy. Similar observations have been made by von Hippel-Pagenstecher[11] in animal experiments when exposing pregnant rabbits to Roentgen radiation. The second group (Unterberger,[12] Reifferscheid,[13] Seynsche[14]), is absolutely opposed to the discussed therapy and bases this condemnation on the results of animal experiments, clinical experience and a study of the literature. Unterberger observed several generations of irradiated butterflies (Oeneria dispar) and found a decrease in size and fertility in the offspring. He goes so far as to suggest a legal prohibition of temporary sterilization by Roentgen rays or radium. Reifferscheid concludes his very thorough discussion of the problem with the statement that as long as a safe performance of temporary sterilization is not proved, it should not be done at all. This is in accordance with the suggestion of Little and Bagg[15] who recommend extreme caution in Roentgen ray and radium therapy of individuals likely to become parents after they have been treated. These authors exposed mice to Roentgen rays (one-fifth of the human erythema dose on each of five successive days) and observed abnormalities of the eyes and feet among the second and third generations. Nuernberger[16] contends, however, that he has seen in his own experiments 104 normal mice in the second and third generations; and only when both parents are irradiated, are malformations to be expected in the offspring. Seynsche reports three cases of mongolism in the children of parents who were exposed to Roentgen rays. The third group of authors, (Werner,[17] Schmitt[18]), is fully aware of the risks one takes in carrying out the treatment of either kind; they suggest, however, trying it in well selected cases after establishing a definite and strict indication (Borell,[19] Schmitt[20]), and proceeding with all possible care.

Some investigators point to the tendency to abortion after treatment. This would agree with the experiments of Schinz[21] who caused a Roentgen ray abortion in animals. Clinically, Ganzoni and Widmer[22] have employed Roentgen rays to produce abortion in women; in 29 out of 34 cases, they succeeded. There was a latent time between treatment and abortion from twenty to fifty-four days. A dose of 250 to 300 Roentgen units effective in the uterus was given. Most women were permanently sterile afterward while some went through normal pregnancies later.

Before we discuss our own indications, 10 cases* will be reported here which were observed during the last year in our department and which belong to this group. The surface dose will be given in each individual case, expressed in per cent of the S.U.D. The radiation used is characterized as follows: 200 K V, 25 M A, 50 cm. F.S.D., 20 by 20 cm. field of entry, 1 mm. copper + 1 mm. aluminum or 0.5 mm. copper + 1 mm. aluminum. A full erythema dose for 1 mm. copper is 550 milliampère minutes, for 0.5 mm. copper, 350 milliampère minutes; Lambda effective (Duane) equal to 0.15 and 0.17 Angstrom units respectively. The depth dose 10 cm. below the surface is approximately 38 per cent for 1 mm. of copper and 34 per cent for 0.5 mm. of copper. (Measured in the central ray.)

(*a*) **Permanent Sterilization.** Case X, 4766.—A married woman, aged forty-one years, never pregnant, four years ago had a cystic tumor of the right tube, the appendix and left tube removed (TB?). Her menstruation has been irregular, scanty and very painful. A full sterilization dose was administered after consultation with the gynecologist had established the indication. Technique: 25 per cent S.U.D. through 1 mm. copper over the anterior and posterior pelvis, three times in weekly doses. Very good result.

Case X, 4717.—A married woman, aged forty-two years, twice pregnant (two children living and well) for the past seven years has had profuse menstruation; four years ago, hemorrhage with each period. Curettage had no effect. Permanent sterilization was deemed advisable considering the age and definite statement of both husband and wife that no further pregnancies were desired. Technique: 75 per cent S.U.D. through 1 mm. copper over the anterior and posterior pelvis in two days. Good result.

Case X, 5173.—A married woman, aged twenty-five years, never pregnant, had an advanced mitral lesion, with menstruation excessive, sometimes bleeding for weeks, extremely painful. Curettement did not show any signs of malignancy. As the internist stated that a pregnancy would be absolutely undesirable, and because the loss of blood influenced the heart lesion very unfavorably, a full sterilization dose was administered after patient and husband signed a request. Four months after the treatment, the periods still appear and are normal; patient complains of backache of moderate degree. Technique: 50 per cent S.U.D. through 1 mm. copper over the anterior and posterior pelvis twice in weekly applications.

* Most patients were referred from the Department of Obstetrics and Gynecology of the University of Michigan (service of Dr. Reuben Peterson).

(*b*) **Temporary Sterilization.** CASE X, 4543.—A married woman, aged thirty-five years, three times pregnant (three children living and well), had excessive menstruation for over three years. Watkin's operation for prolapse was performed and tubes resected one year ago. A Roentgen ray dose of 25 per cent S.U.D. through 1 mm. copper over the anterior and posterior pelvis were given on June 5, July 28, and September 22, 1925. In November, 1925, patient reported that she had three periods during the past five weeks. The first one started after her youngest child was injured. A dose of 20 per cent S.U.D. over the anterior spleen was given; with no menstruation up to the present time. Since last December she has noticed occasional hot flashes; otherwise she is feeling perfectly well.

(*c*) **Small Dose to Ovaries.** CASE X, 5207.—A single woman, aged twenty-three years, for three years had irregular, painful menstruation; one year ago menstruation ceased; at regular time for flow, patient has severe headaches. Examination reveals infantilism of the genital organs. A dose of 10 per cent S.U.D. through 1 mm. copper over the anterior and posterior pelvis was given three times in a period of three months; menstruation has not returned. Symptomatically, the patient is fully improved.

CASE X, 4885.—A single woman, aged nineteen years, menstruation began at the age of fifteen. It is very irregular, but painless. Two years ago the patient sprained her ankle and missed one period after the accident; on return she flowed for three months; curettement stopped the bleeding for two weeks. After three months, she skipped another period followed by two months continuous flowing. Removal of the left ovary improved her condition for four months; then she skipped another period and has been flowing since. A dose of 20 per cent S.U.D. through 1 mm. copper over the anterior pelvis was given twice in a period of two months. When last seen the condition was definitely improved.

CASE X, 4695.—A single woman, aged thirty-one years, menstruation began at age of thirteen. It was very irregular although seldom painful. In August, 1922, following ptomain poisoning, the patient began flowing and had profuse hemorrhages until October. Curettage and packing brought no relief; transfusion was also given; two weeks later the appendix and cysts of the right ovary were removed; two weeks later another curettage and packing were necessary. The bleeding stopped for three weeks and started again; packing brought relief for four weeks. In December, 1923, a suspension was done, the left tube and ovary and a fibroid of the uterus were removed. Shortly after this operation she bled again and had an intrauterine radium treatment. The bleeding gradually decreased and stopped entirely in November, 1924. Hot flashes

and leucorrhea were noticed in March, 1925.* Thyroid and ovarian extracts brought no relief. In August, 1925, she started to hemorrhage again. A dose of 25 per cent S.U.D. through 1 mm. copper was given over the anterior pelvis. The patient has been feeling well since, no hemorrhage, only slight leucorrhea.

CASE X, 5445.—A single woman, aged twenty years, has never menstruated, infantile genital organs. A dose of 10 per cent S.U.D. through 1 mm. copper over the anterior pelvis was given on May 22, 1926 and July 7, 1926; so far no effect has been observed.

CASE X, 5522.—A single woman, aged twenty-three years, began menstruation at the age of fourteen, always irregular; one or more periods a year. The last period occurred three or four years ago. She complains of pain in lower abdomen and frequent headaches. Two treatments of 10 per cent S.U.D. through 0.5 mm. copper over the anterior and posterior pelvis were given on June 14, 1926 and June 28, 1926. No change has been noticed so far.

(*d*) **Spleen Treatment.** CASE X, 4764.—A married woman, aged twenty-nine years, twice pregnant (one child living and well) began menstruation at thirteen years. Since June, 1925, patient has had severe menorrhagia and metrorrhagia. In July, 1925, the appendix, one ovary, and one tube were removed. A dose of 20 per cent S.U.D. through 0.5 mm. copper over the anterior spleen was given and had the desired result.

It is evident from these histories that we believe permanent sterilization† justified only in cases where future pregnancy is either impossible (X-4766) or undesirable from a medical standpoint (X-5173). Between these two extremes there are patients who are approaching the climacteric (X-4717) and have children. After a thorough discussion of the consequences of Roentgen ray treatment with the patient and husband, we believe permanent sterilization permissible if all other therapy fails. Different and much more difficult is the answer to the question of temporary sterilization. There is always the risk of causing permanent amenorrhea—not so great, however, in young women. (See Case X-5173.) We have seen the menstruation reappear even after a full sterilization dose had been administered. The injurious effect on a future pregnancy is, of course, to be considered. It should be stated, however, that Flaskamp[23] compiled from the literature 135 cases up to 1924 and not a single positive proof of abnormality in the offspring due to previous radiation of the mother could be detected. Recently

* The patient entered the University Hospital at this time.

† The term "sterilization" is used in this paper when referring either to the generative or to the menstrual function.

Hickey and Hall* have collected data under the direction of the sex committee of the National Research Council as to the effect of radiation on women who were exposed for diagnostic or therapeutic purposes during pregnancy. From these reports, we take it that 76 pregnant women were exposed for diagnostic purposes; no effect could be seen in a single case; 13 were treated during the first few months of pregnancy, 10 of these came to full term one with twins, in 1 case premature delivery occurred but resulted in the birth of a normal child, and one stillborn.

On the other hand, results of animal experiments suggest caution and it is our opinion that as long as no sure proof of the safe performance of temporary sterilization is available, it should not be recommended as a standard therapeutic procedure where a future pregnancy is probable, not to speak of the difficulty of dosage. Schneider[24] has made an attempt to calculate the doses for temporary sterilization for women of various ages based on clinical observation of the duration of the amenorrhea in the cases of the Gynecological Clinic at Freiburg, which had been compiled by Kadisch[2] who worked under Gauss. Some of these tables (Table I to III) will be published here; the dose is always given in per cent of the skin unit dose and also in E units (Kroenig-Friedrich) effective in the ovaries. The various columns provide for cases of metropathia (Mp), fibroids of the uterus of various size: the first group reaching the symphysis (My 1), the second group reaching the middle between the symphysis and umbilicus (My 2) and the third group reaching the umbilicus or even higher (My 3). For the matter of completeness tables for temporary amenorrhea of various duration (Tables I and II) and also one table for permanent sterilization (Table III) are represented. The original work was done with the assumption that one S.U.D. is equal to 180 E units. For those who prefer to induce temporary amenorrhea with radium, Kupferberg[6] has compiled a dosage table (see Tables IV and V). He used a filter of 1.5 mm. of brass and 1 mm. rubber; the screen was placed in the uterus or the cervix.

TABLE I.—ROENTGEN AMENORRHEA OF FOUR AND A HALF MONTHS (MEAN VALUE BETWEEN FROM ONE TO EIGHT MONTHS).

| Age, yrs. | Mp. | My. I. | My. II. | My. III. |
|---|---|---|---|---|
| 20 to 25 . . . | 24.5 (41.7)† | 24.9 (42.3) | 27.8 (47.4) | 38.2 (65.1) |
| 26 to 30 . . . | 23.3 (39.7) | 23.5 (40.0) | 26.8 (45.6) | 33.9 (57.7) |
| 31 to 35 . . . | 22.2 (37.8) | 22.5 (38.3) | 25.7 (43.7) | 32.1 (54.7) |
| 36 to 40 . . . | 21.1 (36.0) | 21.5 (36.5) | 23.2 (39.5) | 30.5 (51.6) |
| 41 to 45 . . . | 19.9 (34.0) | 20.4 (34.7) | 23.1 (39.4) | 29.3 (48.9) |
| 46 to 50 . . . | 18.8 (32.0) | 19.2 (32.8) | 22.1 (37.6) | 27.2 (46.3) |
| 51 to 55 . . . | 17.8 (30.3) | 18.2 (31.1) | 20.9 (35.6) | 24.6 (43.6) |
| 56 to 60 . . . | 16.7 (28.5) | 17.2 (29.4) | 19.8 (33.8) | 20.9 (40.9) |

* I wish to thank Dr. Hickey and Dr. Hall for the use of their manuscript; for details I refer to the original.

† The first figures give the dose in per cents of the SUD. The figures in brackets represent E units; taken from Schneider.[24]

TABLE II.—ROENTGEN AMENORRHEA OF TWENTY MONTHS (MEAN VALUE BETWEEN FROM EIGHT TO THIRTY-TWO MONTHS).

| Age yrs. | Mp. | My. I. | My. II. | My. III. |
|---|---|---|---|---|
| 20 to 25 | 30.4 (51.9)* | 30.5 (51.7) | 34.9 (59.5) | 44.1 (75.1) |
| 26 to 30 | 29.1 (49.5) | 29.4 (50.0) | 33.4 (56.8) | 42.0 (71.5) |
| 31 to 35 | 27.6 (47.0) | 28.1 (47.7) | 33.0 (54.3) | 40.0 (68.3) |
| 36 to 40 | 26.3 (44.8) | 26.8 (45.5) | 30.5 (53.7) | 37.8 (64.4) |
| 41 to 45 | 24.9 (42.4) | 25.4 (43.3) | 28.9 (49.2) | 35.9 (61.1) |
| 46 to 50 | 23.5 (40.0) | 24.1 (41.1) | 27.4 (46.6) | 33.5 (57.7) |
| 51 to 55 | 22.1 (37.7) | 22.9 (38.9) | 26.1 (44.4) | 32.0 (54.4) |
| 56 to 60 | 20.8 (35.5) | 21.1 (36.6) | 24.8 (42.2) | 30.0 (51.1) |

* See footnote of Table I; taken from Schneider.[24]

TABLE III.—PERMANENT ROENTGEN AMENORRHEA.

| Age, yrs. | Mp. | My. I. | My. II. | My. III. |
|---|---|---|---|---|
| 20 to 25 | 31.9 (54.4)* | 32.2 (54.8) | 37.1 (63.2) | 46.1 (78.4) |
| 26 to 30 | 30.7 (52.2) | 30.9 (52.6) | 35.2 (60.6) | 44.1 (75.1) |
| 31 to 35 | 29.4 (50.0) | 29.6 (50.4) | 34.1 (58.0) | 42.2 (71.8) |
| 36 to 40 | 28.1 (47.8) | 28.3 (48.1) | 32.6 (55.5) | 39.6 (67.6) |
| 41 to 45 | 26.7 (45.5) | 26.9 (45.8) | 30.8 (52.5) | 37.7 (64.3) |
| 46 to 50 | 25.0 (43.6) | 25.5 (43.4) | 29.4 (50.0) | 35.8 (61.0) |
| 51 to 55 | 23.9 (40.8) | 24.2 (41.2) | 27.8 (47.4) | 33.9 (57.7) |
| 56 to 60 | 22.4 (38.2) | 22.9 (39.0) | 26.3 (44.8) | 32.0 (54.4) |

* See footnote of Table I; taken from Schneider.[24]

TABLE IV.—TEMPORARY AMENORRHEA (MEAN VALUE BETWEEN FROM THREE TO TWELVE MONTHS).

| Age, yrs. | Mp. | My. I. | My. II. | My. III. |
|---|---|---|---|---|
| 20 to 25 | 600* | 800 | 1000 | 1200 |
| 26 to 30 | 600 | 800 | 1000 | 1200 |
| 31 to 35 | 550 | 750 | 950 | 1150 |
| 36 to 40 | 550 | 750 | 950 | 1150 |
| 41 to 45 | 500 | 700 | 900 | 1100 |
| 46 to 50 | 500 | 700 | 900 | 1100 |
| 51 to 55 | 500 | 650 | 850 | 1050 |
| 56 to 60 | 500 | 650 | 850 | 1050 |

* Dosage in milligram hours; taken from Kupferberg.[6]

TABLE V.—TEMPORARY AMENORRHEA (MEAN VALUE BETWEEN FROM TWELVE TO THIRTY MONTHS).

| Age, yrs. | Mp. | My. I. | My. II. | My. III. |
|---|---|---|---|---|
| 20 to 25 | 1200* | 1600 | 2000 | 2400 |
| 26 to 30 | 1200 | 1600 | 2000 | 2400 |
| 31 to 35 | 1200 | 1400 | 1800 | 2200 |
| 36 to 40 | 1100 | 1400 | 1800 | 2200 |
| 41 to 45 | 1100 | 1200 | 1600 | 2000 |
| 46 to 50 | 1100 | 1200 | 1400 | 1800 |
| 51 to 55 | 1000 | 1100 | 1200 | 1600 |
| 56 to 60 | 1000 | 1100 | 1200 | 1400 |

* Dosage in milligram hours; taken from Kupferberg.[6]

There is no question that these tables cannot be considered as permanent; the authors themselves state very definitely that they have been worked out on the basis of observations made on a limited number of patients and should be considered, therefore, as a working basis. This should confine the application to institutions where facilities for exact measurement of the administered dose are provided, followed by a complete clinical study of the individual case. Suitable cases are very carefully selected types of inflammatory diseases of the adnexa, mild forms of pulmonary tuberculosis with excessive or painful menstruation and women who have had frequent pregnancies without reasonable interval.* Only one case in our experience was treated accordingly (X-4543); in several others it was considered, but we could not recommend it. In order to prevent injuries to future pregnancies Penzoldt[25] has suggested inducing abortion in women where conception took place during the first four months after a temporary sterilization dose has been administered.

The last group of ovarian dysfunctions comprises all of the disturbances of the menstrual period which cannot be traced by the most careful examination to any definite cause. We feel that everything else in the way of symptomatic therapy should be given a fair trial before radiation is considered (Martius[26]). This indication was present in 5 of our cases (X-5207, X-4885, X-4695, X-5445, X-5522) and 2 patients were improved under treatment, while in another case (X-4764) an exposure of the spleen had the desired effect. In this connection we should like to mention Mansfeld[27] who recommended treating only one ovary by carefully protecting the other side. In young women it is possible, as mentioned before, that even after the administration of a full castration dose not all follicles may have been destroyed; furthermore a small amount of scattered radiation will reach the ovary on the opposite side. On the other hand, Wagner and Schoenhof[28] have recently published the results of their histologic studies of ovaries of patients who had to undergo an abdominal operation and were treated before with from one-tenth to one-fourth of the sterilization dose. From one day to several weeks later, the ovaries were taken out and examined microscopically; no changes could be detected which might point to a destructive effect of such doses on ovarian tissue.

**Conclusions.**† 1. Study of the literature reveals that no agreement has so far been reached on the question of producing temporary sterilization by radiation or of treating the ovaries with small doses of Roentgen rays or radium to correct dysfunction.

2. Our indications in these cases are explained; it is advisable

* Compiled from reports published on this subject.

† The author is indebted to Dr. Norman F. Miller for his great interest in this paper and for many valuable suggestions.

to proceed with great caution and leave the performance of such treatment to laboratories equipped to measure the dose exactly.

3. Temporary sterilization by radiation and small doses of Roentgen rays or radium to the ovaries cannot be recommended at present as a recognized therapeutic measure; this work is still in the experimental stage.

4. Further study of the problem is essential; the publication of all such cases with the exact dose of treatment given including the duration of amenorrhea, later pregnancies, and other necessary data is urged. This will not only allow us to judge finally the value of this therapy but also furnish the figures for a tabulation of the correct dose.

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## THE BACTERIUM CAUSING RHEUMATIC FEVER AND A PRELIMINARY ACCOUNT OF THE THERAPEUTIC ACTION OF ITS SPECIFIC ANTISERUM.*

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Acute rheumatic fever has long been established as a clinical entity. Tonsillitis, arthritis, endocarditis, myocarditis, pericarditis and chorea are outstanding clinical manifestations attending this rather complex syndrome. More recently the part played by acute rheumatic fever in established chronic heart conditions has come to be more and more appreciated. There has been much evidence offered to establish the tendency to chronicity as one of its most important characters. This latter has centered chiefly about the cardiac involvement (Danielapolu[1]). Many claim that the cardiac infection is established as a chronic condition in very many instances following the primary acute attack of the disease (Bezançon and Weil[2]). The part played by the specific virus of rheumatic fever in the etiology of the chronic arthritides has not been emphasized chiefly because these conditions do not lend themselves so readily to a clinical classification.

The belief that rheumatic fever is an infectious disease has much in its support. Aside from what might be termed the characteristic nature of the clinical characters of the acute condition are the observations on its seasonal prevalence as well as those on its cyclic appearances in what appear to be low-grade epidemics (Newsholme[3]).

* Contrary to our usual custom, we have published this article at the earliest possible date, believing that it may contain information of the highest importance, which should be investigated by others, as soon as possible.—The Editors.

The familial appearance of multiple cases is also a pertinent observation in this connection (St. Lawrence;[4] Faulkner and White[5]).

The association of the onset of the disease with attacks of acute tonsillitis, together with the many bacteriologic studies associating various streptococci with the etiology of tonsillitis, has led to the belief in many quarters that a particular group of streptococci is concerned as the etiologic factor in rheumatic fever. From the appearance of a streptococcus so constantly in the valvular vegetations of ulcerative endocarditis which has as its chief antecedent acute rheumatic fever, this association of streptococci with the cause of rheumatic fever has been further emphasized (Clawsen[6]). Much good work has been done in connection with the pathology of rheumatic endocarditis and ulcerative endocarditis, which has served to differentiate the two conditions quite definitely. From the clinical standpoint, however, the transition from the rheumatic type into the secondary streptococcus type cannot be definitely recognized. Various types of streptococci grown from the blood of patients with rheumatic fever has been studied (Clawsen[6]). The streptococcus described by Poynton and Payne[7] deserves first mention. This organism has not been described in sufficient detail to permit its recognition as a distinct biologic species. Others have described streptococci associated with rheumatic fever variously as Streptococcus viridans, Streptococcus anhemolyticus, Streptococcus nonhemolyticus and so forth.

The serologic study of the strains thus isolated has been disappointing in that no dominant immunologic group could be identified (Clawsen,[8] Kreidler[9]). Yet many observations on the production of arthritis and cardiac lesions in animals are on record from the inoculation of these diverse strains of streptococci (Cole;[10] Jackson;[11] Cecil[12]).

The exact reproduction of the microscopic lesion of the myocardium in rheumatic fever (Aschoff[13]) has not, however, been accomplished. Here again there is a question of expert opinion, for it is noteworthy that some of these lesions in animals do closely resemble the Aschoff nodules (Coombs;[14] de Vecchi;[15] Jackson;[11] Cecil[12]). The terms anhemolytic streptococcus and streptococcus viridans have been used by some synonomously. Hence confusion has arisen in conjunction with the question of identifying a streptococcus which has been used by others in the production of experimental arthritic and cardiac lesions.

We are presenting in this report the description of a streptococcus which has a specific immunologic identity; which has been isolated in the first instance from the blood of a patient suffering from rheumatic fever; which has been cultured in each instance from the throats of patients with rheumatic fever; which is capable of producing characteristic arthritic and cardiac pathology in rabbits, including Aschoff nodules; and with which a specific therapeutic serum may be prepared which is effective in terminating the toxemia and other clinical manifestations in the patient suffering from acute

rheumatic fever. For this organism the name Streptococcus cardioarthritidis, *spec. nov.*, is suggested. This name, for the sake of brevity will appear throughout this report.

**Isolation of the Streptococcus Cardioarthritidis.** Since all of the experimental work reported in this paper has been done with the first strain of Streptococcus cardioarthritidis isolated, it will be of interest to outline briefly the circumstances attending its isolation.

The strain was isolated from a blood culture made on April 5, 1926. The patient (C. L., Medical Ward 335, Phila. Gen. Hosp.) was an adult colored man, whose illness began with a tonsillitis on March 15, 1926. The joint involvements began several days subsequent to the onset of the tonsillitis. The character of the joint involvement, its tendency to involve successively various large joints, the tendency to profuse sweating and the response to salicylate medication, all tended to confirm the clinical diagnosis of acute rheumatic fever. The culture was made in infusion broth (PH 7.6) and showed growth turbidity on the ninth day of incubation. Smears showed a Gram positive coccus in short chain formations. In subculture upon the surface of horse blood agar small, gray colonies producing absolutely no change upon the blood of the medium were revealed. This strain was designated R 1.

This patient had a tonsillectomy performed on April 10, 1926, following which a slight return of the joint involvements was recorded. Blood was obtained from the patient on April 16, 1926. The serum agglutinated the strain in dilutions up to 1 to 320.

**Animal Experiments.** These observations prompted tests for pathogenicity. Accordingly, young broth cultures of the organisms were inoculated into each of two rabbits. In these rabbits widely divergent results were obtained, as appears in following proctocols:

PROTOCOL I. April 19, 1926. Rabbit R 1/1. Gray rabbit (left ear marked with picric acid).

April 19, 1926. One cubic centimeter of broth culture injected intravenously. No effect on animal.

April 27, 1926. Growth from 25 cc. broth injected intravenously. No effect other than slight indisposition on day following the injection.

May 4, 1926. Growth from 25 cc. broth injected intravenously. No effect on animal.

May 10, 1926. Test bleeding: Serum shows high titer.

May 13, 1926. Animal bled from heart 10 cc. and the serum preserved.

May 14, 1926. Seven billion streptococci injected intravenously. No effect on animal.

May 28, 1926. Animal exsanguinated by cardia-puncture under aseptic conditions. Forty-five cubic centimers of serum was obtained. Agglutination titer, 1 to 20,480. The serum was filtered through a Mandler filter and preserved with 0.3 per cent of phenol. Forty cubic centimeters was bottled for use as a therapeutic serum. (This serum was used in treating Patient I. See clinical abstracts.)

PROTOCOL II. April 19, 1926. Rabbit R 1/2. Gray rabbit in fair general condition, but not as well nourished as the above rabbit. It was injected intravenously, as follows:

April 19, 1926. One cubic centimeter broth culture injected intravenously. No effect on animal.

April 27, 1926. Growth from 25 cc. of broth injected intravenously. Arthritis developed.

April 30, 1926. The animal appears very sick. It is knocking its head against the side of the cage and is apparently in great pain. Examination shows the right knee to be swollen, red and tender. The joint itself appears looser than normal, perhaps because of an excess of fluid in the joint cavity The periarticular tissues and the bursa about the joint appear to be filled with fluid. Observation made at 4 P.M.

May 1, 1926. 9.30 A.M. The animal is still very sick and in much pain. Both knees are now swollen, red and tender. The hair was clipped away from these joints and photographs were made (Figs. 1 and 2). At noon a cardia-puncture was made and blood obtained for culture. This culture remained sterile after ten days' incubation. Both knee joints were aspirated and cultures made of the small amount of fluid obtained. These cultures likewise remained sterile.

May 2, 1926. The animal's general condition has improved. There appears to be less pain and tenderness. The knee joints are large, but the redness over them is subsiding. The animal can use the hind legs slightly.

May 3, 1926 to May 10, 1926. The general condition of the animal continues to improve. On the latter date the joints are still enlarged and stiff. They can be used very little. The acuteness of the process is declining.

May 12, 1926. Condition of the joints is improving gradually. There has been a slight decrease in size.

May 14, 1926. Joints are still enlarged but the tenderness seems to have disappeared. On this date, the animal was reinjected with 7 billions of streptococci (Strain R1) intravenously.

May 15, 1926. Animal is very sick. No exacerbation of joint symptoms.

May 16, 1926. Animal is very sick. No exacerbation of joint symptoms.

May 17, 1926. Animal is very sick. When taken from the cage it attempted to run across the room, but fell over on its side exhausted and gasping for breath. Heart pulsations cannot be palpated. Animal is apparently dying. The ear vein was opened, but blood failed to flow. Thirty minutes later the animal remains in the same condition. It is now chloroformed and necropsy performed at once.

NECROPSY. Gross Pathology: Marked atrophy of skeletal muscles; areas of focal necrosis in the liver; subacute proliferative arthritis of both knees; marked dilatation, and flabbiness of the heart muscle; several small patches of bronchial pneumonia; inflammatory infiltration in the patellar ligament.

MICROSCOPIC PATHOLOGY (Report by Dr. J. L. Goforth):

*Heart Muscle.* Marked acute degeneration. No Aschoff nodules. Here and there among the muscle fibers appear collections of large mononuclear cells. These do not appear to be associated with the bloodvessels, nor do they resemble Aschoff bodies, but their finding warrants a diagnosis of multiple chronic focal inflammatory areas in the myocardium.

*Skeletal Muscle* (thigh). Marked acute degeneration. No Aschoff bodies. Several small, focal abscesses were found.

*Lungs.* Patches of purulent, confluent bronchopneumonia. Moderate congestion and edema in lower portions of lungs.

*Liver.*—Marked cloudy swelling throughout. Multiple abscesses and small areas of focal necrosis.

*Kidney.* Cloudy swelling. No abscesses.

*Spleen.* Marked congestion only.

*Adrenal.* Appears normal.

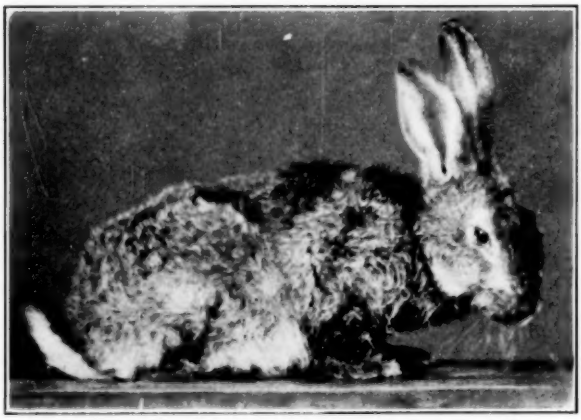

FIG. 1.—Photograph of Rabbit R 1/2, May 1, 1926.

FIG. 2.—Acute arthritis of both knees in Rabbit R 1/2, May 1, 1926

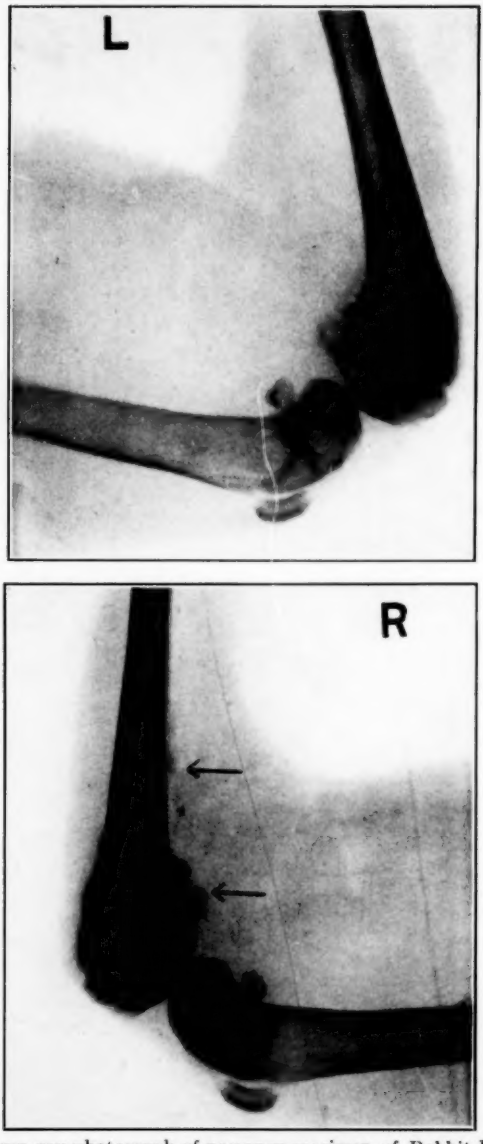


FIG. 5.—Roentgen ray photograph of necropsy specimen of Rabbit R 1/2, showing new-bone formation.

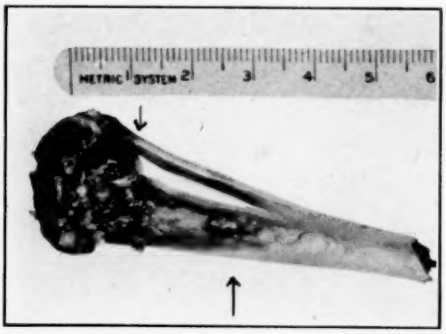


FIG. 6.—Tibia and fibula of Rabbit R 1/2, showing locations of new-bone formation.

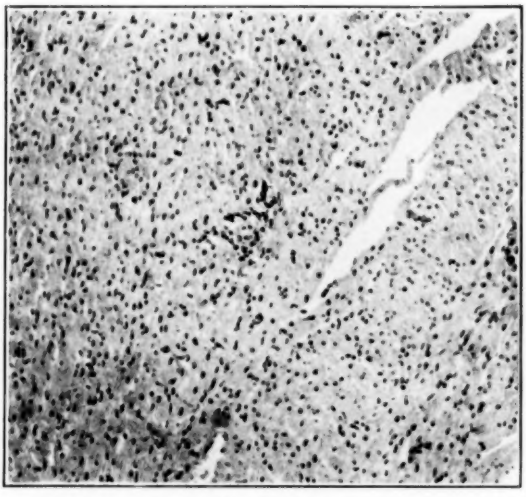

FIG. 7.—Aschoff-like body in heart muscle. × 100. Rabbit R 1/6.

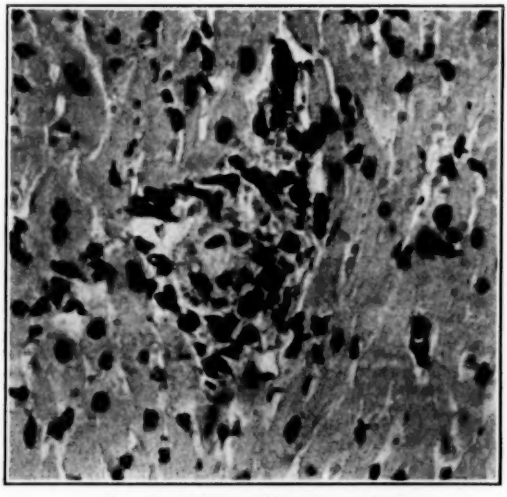

FIG. 8.—Same as Fig. 7. × 450.

FIG. 9.—Photomicrograph of Streptococcus cardioarthritidis from twenty-four-hour broth culture.

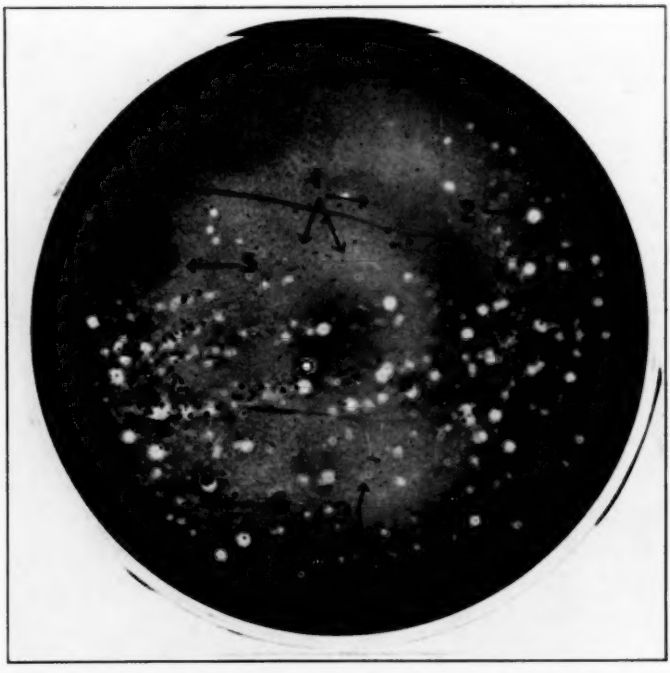

FIG. 10.—Direct throat culture on blood agar, showing: 1, Streptococcus cardioarthritidis; 2, hemolytic streptococcus; 3, Streptococcus viridans; 4, Staphylococcus aureus; 5, Bacillus proteus (spreader); 6, Micrococcus catarrhalis.

*Patellar Ligament.* The synovial membrane is thickened, giving the picture of chronic inflammation. A deposit within the ligament consists chiefly of lipoid-containing tissues, covered by thickened synovial mem-

FIG. 3.—Arthritis of both knees at necropsy of Rabbit R 1/2, May 17, 1926.

FIG. 4.—Necropsy specimen, Rabbit R 1/2, showing atrophy of skeletal muscles, May 17, 1926.

branes, all of which are chronically inflamed. There is a moderate mononuclear infiltration of the adjacent ligamentous structures.

*Bone Marrow.* The sinuses are filled with erythrocytes. There appears to be a moderate degree of activity, chiefly myeloid.

PROTOCOL III. May 4, 1926. Rabbit R 1/3. A white, female rabbit, weighing 2290 gm., was inoculated intravenously with one-third of the total growth of 100 cc. of infusion broth, after twenty-four hours of incubation. No symptoms followed this injection.

May 8, 1926. The rabbit received the entire twenty-four-hour growth obtained in 100 cc. of infusion broth at 12.30 P.M. The following morning, the animal was found dead, but in a good state of preservation. A necropsy showed the following findings:

*Liver.* Very large and studded with small, white abscesses. The spleen is small and of dark color. The kidneys are intensely engorged. The heart, both auricles, are dilated with dark blood clots, and a similar clot appears in the right ventricle. There is no abnormality of the heart valves. The arch of the aorta showed a rather extensive atheromata. The lungs contained air throughout, but showed deeply mottled areas. The pleural and peritoneal structures are normal. The heart muscle appeared firm and normal.

MICROSCOPIC PATHOLOGY (report by Dr. J. L. Goforth):

*Heart.* The muscle fibers are swollen, granular in appearance, and have lost their striations. No Aschoff nodules present. Diagnosis: Acute parenchymatous degeneration.

*Lungs.* Marked congestion, multiple, small, early focal necrosis. (Beginning abscesses.)

*Spleen.* Congestion. There is diffuse phagocytosis of blood pigment. The picture is that of an acute splenitis, but no focal necroses nor abscesses are seen.

*Kidney.* Marked cloudy swelling and congestion.

*Liver.* The liver is studded with small patches of necroses which are more frequently seen about the central veins than about the portal veins. These areas are made up of cell detritus, (disintegrating polymorphonuclear and hepatic cells). Congestion and marked acute diffuse parenchymatous degeneration are also present. Diagnosis: Multiple necroses. The general picture is that of an acute intoxication. Because of the multiple focal necroses in the lungs and liver, a bacteremia can be assumed.

PROTOCOL IV. May 19, 1926. Rabbit R 1/4. Strain R I was grown in broth for twenty-four hours, the culture centrifugalized, and the bacteria suspended in saline in a concentration of 7.5 billions per cubic centimeter. This rabbit, a brown female, weighing 1865 gm., was injected intravenously with 11 billions of the bacteria at 4.30 P.M. At 9 P.M. the rabbit appears listless and sick. Temperature 104.8° F., and the leukocytes had declined from 5900 at 4.30 P.M., to 2300 at this time.

May 21, 1926. The rabbit is very sick and does not eat. It sits quietly in the cage. The temperature ranged from 104.8° to 106.8° F. and the leukocyte count was 3800 at 3.30 P.M.

May 22, 1926. The rabbit shows marked excitability but is very weak. It lies on the abdomen with the hind legs to one side. The head is held high and the nose pointed out horizontally. The head is constantly in motion in an anteroposterior axis, thus presenting a coarse tremor which resembles that of paralysis agitans. When the animal is disturbed there appears a marked exaggeration of this symptom and choreiform tremors develop in the extremities. The animal makes frantic efforts to run away when turned loose on the lawn, but after running a dozen hops, or more, it becomes exhausted and falls on its side, resting nose and head upon the ground.

May 23, 1926. The animal is absolutely prostrated. It lies quietly for a minute or so and then is seized with choreiform movements of the legs. Such seizures occur at irregular intervals and are much aggravated if the

animal is disturbed. The animal refuses to eat and is very much dehydrated. It is given 30 cc. of normal saline subcutaneously.

May 24, 1926. The animal lies in a comatose condition. The temperature is subnormal, the respirations slow. It is given 30 cc. of 10 per cent glucose in normal saline, subcutaneously, and is placed in an incubator room at 35° C. This revived the animal slightly, so that the temperature rose to normal and the respirations became regular and more rapid. In the late afternoon, the animal took a little water, by mouth.

May 26, 1926. The animal is still prostrated and in much the same condition as yesterday. Choreiform movements are still very marked. The animal eats sparingly of greens, held to its mouth and takes a fair amount of water.

June 1, 1926. The animal is still prostrated but eats ravenously of food when presented to its mouth. Lateral nystagmus is noted for the first time.

June 4, 1926. The animal lies on its left side, but makes attempts to crawl.

June 7, 1926. The animal sits up of its own efforts for short periods, but tends to fall to the left side.

June 9, 1926. The animal sits up at will. It attempts to hop about, but falls to the left side. Choreiform movements are still very marked.

June 12, 1926. The rabbit presents some stiffness of the hind legs and shows upon examination enlargement of the left ankle joint.

June 15, 1926. The animal's condition is improving, slightly, and now enlargement of several digital joints of the right hind foot is apparent. There has been to date a very marked atrophy of the skeletal muscles.

June 18, 1926. A subcutaneous fluctuating mass on the flexor aspect of the right ankle appears. The skin covering this is reddened.

June 21, 1926. Thick, viscid, purulent material is obtained upon aspiration of the collection mentioned above. Cultures of this fail to show any bacteria.

This animal is alive at the present date (December 9, 1926). It has not regained its original weight. The skeletal muscles are still markedly atrophic. The nodding spasm of the head is observed as an intention tremor, only when the animal attempts to eat or drink.

*Summary.*—This animal has shown a central nervous system lesion immediately following an intravenous injection of Streptococcus cardioarthritidis. Careful nursing helped it to survive the acute stage of the illness. Approximately three weeks after the injection, a rather low-grade arthritis appeared involving multiple joints in succession. Approximately seven months after the injection, the animal shows chronic arthritis and stiffness of the hind legs, skeletal muscle atrophy and an intention tremor. Further details in connection with this animal must await a subsequent report.

Protocol V. Rabbit R 1/6. Brown male. On July 8, 1926, this animal received an intravenous injection of 12 billions of viable streptococci (Strain R 1). A careful clinical study including observation of joints, temperature readings, the animal's weight and complete blood counts, was made. In summary there appeared a leukopenia immediately following the injection, which was followed by leukocytosis. There appeared following the injection a decrease in the number of erythrocytes and a corresponding decrease in hemoglobin, from 12.1 gm. per 100 cc. of blood prior to the injection, to 9.1 gm. eleven days after the injection. From this point a slow improvement in the hemoglobin content of the blood was noted. On August 9, the animal's serum titer in the agglutination reaction with the hemologous antigen, was 1 to 20. On this date it received a second intravenous injection of 12 billions of living organisms, strain R 1. Aside

from a temperature and leukocytic reaction, little else was observed to follow this injection. On August 18, 1926, the animal received a third intravenous injection of 9 billions living organism (Strain R 1). The morning of August 19, 1926 the animal was found dead.

*Necropsy.* The organs showed throughout marked congestion of an acute bacteremia. In the liver were small focal abscesses. The heart muscle was flabby. On the under surface of the mitral valve there appeared two small, white abscesses. For present purposes the histology of the heart muscle, alone, will be presented. The heart muscle fibers were swollen and granular in appearance and had lost their striations. Scattered throughout the heart muscle are large mononuclear cells occurring singly, or in small groups, but without relation to the bloodvessels. Several places in the sections studied there occurred collections about the bloodvessels which resemble Aschoff bodies. One such Aschoff body is illustrated in Figs. 7 and 8. A section through the mitral valve shows a small, well-circumscribed abscess at the junction of the valve and the mural wall. The valve itself is otherwise normal.

**Isolation Methods.** Two strains of Streptococcus cardioarthritidis were obtained from blood cultures. These cultures were made by adding from 3 to 5 cc. of the patient's blood to bottles containing from 75 to 90 cc. of plain beef infusion broth (PH 7.6). The initial growth turbidity occurred in the first case upon the ninth day of incubation and in the second upon the nineteenth day of incubation.

The throat cultures were prepared by inoculation of material collected on sterile cotton swabs upon the surface of blood-agar plates. The colonies appeared after eighteen to twenty-four hours incubation.

The cultures of feces were made by the direct inoculation of light emulsions of the material upon the surfaces of blood-agar plates. At the same time 3 tubes of broth containing varying amounts of acid fuchsin were inoculated with a loopful of the same emulsion. These tubes after twenty-four-hours incubation were seeded upon the surfaces of blood-agar plates. This latter indirect method is the more reliable since the interfering profuse growth of colon bacilli is suppressed by it.

After the cultures are obtained in pure growth, broth tubes may be seeded and the organisms tested against a stock of agglutinating serum, in the same manner by which typhoid bacilli are identified by agglutination with their specific antiserum.

**Serology of Strains.** A portion of the serum prepared from rabbit R 1/1, which agglutinated homologus R 1 antigen in dilutions up to 1 to 20,000, was used for identification of the strains of the organisms obtained in subsequent cultures.

As the strains were isolated they were grown for from eighteen to twenty-four hours in infusion broth and tested for agglutination against this serum, using it in 1 to 2000 dilution, that is at one-tenth of its full titer, a dilution not likely to pick up associated serologic strains in a group reaction.

The cross agglutination and absorption reactions, as well as a detailed study of the serology of nonhemolytic streptococci from various sources will be the subject of a detailed report based upon work now in progress. It is possible that this work will reveal different serologic type strains of Streptococcus cardioarthritidis. Suffice here to say that all of the strains listed in Table I were agglutinated by the antiserum prepared with Strain R 1.

**Biologic Reactions of Streptococcus Cardioarthritidis.** Table II presents the carbohydrate fermentation reactions, the action on milk, on gelatin and the indol tests made on the first 20 strains of the organism isolated. Two strains of nonhemolytic streptococci, *Fol.* and *Arrig.*, which bear no serologic relationship to the Streptococcus cardioarthritidis are included in the table for the sake of permitting comparisons.

TABLE I.—CATALOGUE OF STRAINS OF STREPTOCOCCUS CARDIOARTHRITIDIS.

| Date isolated, 1926. | Patient. | Strain number. | Source. | Diagnosis of patient's condition. |
|---|---|---|---|---|
| April 5 | C. L. | R 1 | Blood | Acute rheumatic fever. |
| 19 | M. M. | R 2 | Feces | Chronic arthritis. |
| May 19 | C. O. | R 3 | Throat | Subacute rheumatic fever. |
| 24 | A. F. | R 4 | Throat | Chronic arthritis. |
| 24 | J. McB. | R 5 | Throat | Acute rheumatic fever. |
| 24 | J. J. | R 6 | Throat | Rheumatic fever and pericarditis. |
| June 15 | M. B. | R 7 | Throat | Chronic arthritis. |
| 15 | M. D. | R 8 | Feces | Chronic arthritis. |
| May 8* | C. O. | R 9 | Blood | Subacute rheumatic fever. |
| 19 | R. W. | R 10 | Throat | Vague rheumatic pains. |
| 21 | C. S. | R 11 | Throat | Vague rheumatic pains. |
| 22 | J. C. | R 12 | Feces | Chronic arthritis. |
| 22 | M. G. | R 13 | Throat | Chronic arthritis. |
| July 28 | L. A. J. | R 14 | Throat | Chronic arthritis. |
| Aug. 2 | M. W. | R 15 | Throat | Acute nephritis. |
| 2 | J. L. W. | R 16 | Throat | Myositis. |
| 2 | M. C. | R 17 | Extirpated tonsils | ? |
| 7 | H. G. | R 18 | Throat | Chronic arthritis. |
| 14 | M. M. | R 19 | Throat | Acute chorea. |
| Oct. 9 | M. P. | R 20 | Throat | Chronic arthritis. |
| Nov. 26 | E. K. | R 21 | Throat | Acute myositis. |
| 26 | J. C. | R 22 | Throat | Acute rheumatic fever. |
| 22 | E. M. | R 23 | Throat | Recurrent acute rheumatic fever. |
| 27 | F. B. | R 24 | Throat | Gonorrheal arthritis. |
| 29 | A. B. | R 25 | Throat | Acute rheumatic fever and pericarditis. |
| Dec. 4 | E. G. | R 26 | Throat | Acute chorea. |
| 4 | A. R. | R 27 | Throat | Acute rheumatic fever. |
| 4 | M. H. | R 28 | Throat | Chronic arthritis. |
| 6 | H. L. | R 29 | Throat | Acute rheumatic fever. |
| 7 | D. C. | R 30 | Throat | Convalescent pericarditis. |
| 8 | M. A. | R 31 | Throat | Chronic arthritis. |

* See R 3.

Strain *Fol.* was isolated from feces of the patient suffering from chronic osteoarthritis. Strain *Arrig.* was obtained in throat culture from a patient afflicted with sciatica.

The outstanding feature of Table II is the remarkable constancy of the fermentation reactions. Lactose alone is not uniformly affected. A second feature is the uniform fermentation of inulin. If one wishes for purposes of orientation to apply Holman's[16] classification of streptococci of these 20 strains, they would fall into two little studied groups designated by him as "streptococcus mitis with inulin" and "streptococcus equinus with inulin." It is evident from his original report that streptococci which ferment inulin can be regarded as streptococci only after adequately proving the absence of the characteristic properties of pneumococci. It appears further that the streptococci which he has included in these two groups do, in many instances, produce a green discoloration about the colony on blood agar. It is doubtful, therefore, whether a streptococcus such as the Streptococcus cardioarthritidis, which produces absolutely no change on blood media, should be included in these groups.

TABLE II.—FERMENTATION OF CARBOHYDRATES, ACTION OF MILK, GELATIN AND FORMATION OF INDOL. STREPTOCOCCUS CARDIOARTHRITIDIS.

| Strains. | R 1. | R 2. | R 3. | R 4. | R 5. | R 6. | R 7. | R 8. | R 9. | R 10. | R 11. | R 12. | R 13. | R 14. | R 15. | R 16. | R 17. | R 18. | R 19. | R 20. | Fol. | Arrig. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Glucose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lactose | − | + | + | + | − | − | − | + | + | + | − | + | + | + | + | + | − | + | + | − | + | + |
| Sucrose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + |
| Mannitol | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | + |
| Inulin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + |
| Raffinose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + |
| Salicin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + |
| Milk | − | AC | AC | AC | − | − | − | AC | AC | AC | − | AC | AC | AC | AC | AC | − | AC | AC | − | AC | AC<br>Pept. |
| Gelatin | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | Liqf. |
| Indol | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | Pos. |

+, fermentation of the carbohydrate with acid formation; −, no action on the carbohydrate; AC, acid formation and coagulation; Pept. digestion of clot.

The carbohydrate fermentation reactions appear to have little value in the classification of streptococci. In this instance we have 20 different strains which show an immunologic identity, but which, nevertheless, show a slight discrepancy in their actions upon lactose.

**Description of Streptococcus, Cardioarthritidis Based upon Observations of the First 20 Strains Isolated.** The organism is a spherical Gram positive coccus which in fluid medium yields diffuse growth and shows short chain formations. It is readily stained by the ordinary analine dyes. It is nonmotile, aërobic and facultative anaërobic. Neither flagellæ, spores nor capsules are identified. It is of rather constant, uniform size, varying from 0.7 $\mu$ to 1.2 $\mu$ in diameter. The optimum temperature for growth is 37° C., but growth at lower temperatures occurs. The organism is insoluble in bile. Heated to 60° C. it is killed in from six to ten minutes. Growth fails to occur on any but the richer media. On coagulated serum, very small, moist, smooth, flattened, white colonies appear. There is no digestion of the medium. In plain infusion broth, pH 7.6, a diffuse turbidity develops in twenty-four hours with slight sedimentation. Upon longer periods of incubation, slight slumping occurs with sedimentation and a tendency toward clearing of the supernatant fluid. The different strains differ only slightly in the tendency to clumping upon growth in broth, some requiring longer periods of incubation than others. However, all show diffuse growth after eighteen to twenty-four hours. In infusion broth twenty-four-hour growth corresponds to from $\frac{1}{4}$ to $\frac{1}{3}$ of a billion per cubic centimeters of broth. The addition of glucose to the broth in amounts varying from 0.1 per cent upward very greatly enhances the growth. Growth of from 1 to 3 billions per cubic centimeter may be obtained in this manner in twenty-four-hour cultures. The growth remains diffuse in twenty-four-hour cultures in glucose broth, but after several days incubation it tends to clump and settle out. The media containing glucose is acidified without gas formation.

In Dunham's peptone, plain extract broth (pH 6.6) plain extract agar (pH 6.6) growth fails. On the veal-broth-brain agar (Pelouze and Viteri)[11] (pH 7.6) good growth is obtained. The colonies appear smooth, round, dome-shaped and transparent. The bases are round and edges of colonies regularly outlined.

In carbohydrate media, glucose, sucrose, inulin, raffinose and salicin have been fermented with acid formation but no gas in each instance. Mannitol has not been fermented in any instance, and lactose has been fermented by 14 of the strains, and not fermented by 7.

The appearance on blood agar is most characteristic. Growth has been studied on plain infusion agar, enriched by 5 per cent by volume of defibrinated horse blood. In preparing blood agar, the blood is evenly distributed and the media poured in thin layers (2 to 3 mm. deep) in Petri dishes. Upon such media after twenty-four hours, and indeed after longer periods, no change in the hemoglobin is effected. There is neither the slightest hemolytic action nor any tendency to the formation of methemoglobin. Green or dirty brown discoloration about the colonies is entirely absent. In stock cultures kept on blood agar in the refrigerator for some weeks, at times, it has been noted that the entire blood slant has changed to a brown color. This does not occur consistently and is believed not to be a result of the products of bacterial growth, unless it be a change toward an acid reaction in the media. The colonies on blood agar by transmitted light appear a characteristic opaque red-brown color. This opacity of the colony on blood agar is characteristic and serves to differentiate it easily from colonies of Micrococcus catarrhalis, Bacillus influenzæ and staphylococcus, by this examination alone (Fig. 10). By reflected light the colonies are a gray-white. They have regularly outlined, round bases and vary in

size from pin point to about 1 mm. in diameter. Upon touching them with an inoculated wire, they are of a soft, pasty consistency. They do not shove along the surface of the agar nor are they lifted off in their entirety.

**Preliminary Report of the Preparation and Therapeutic Action of the Antiserum in Rheumatic Fever.** PREPARATION OF THERAPEUTIC SERUM: The first serum used in the treatment of a patient was obtained on May 28, 1926, from an immunized rabbit (R 1/1; see protocol). This animal had received four intravenous injections of viable organisms grown in broth cultures. It showed an unusual response to rather irregularly spaced injections, in that it yielded a serum showing a titer to the homologous antigen of over 1 to 20,000. Patient I (see case histories) was treated with 20 cc. of this serum by intramuscular injection. There was a termination of the clinical symptoms of chorea and arthritis by crisis. Upon the strength of this very favorable result, it was determined to immunize a horse. Accordingly, a healthy horse of between seven and eight years of age was obtained. The complement-fixation test for glanders with its serum proved negative. This animal received killed cultures of Strain R 1, first subcutaneously and later intravenously, over a period of two months. The response, as judged by the agglutinin titer of the serum from time to time, was good. The agglutinin titer rose from 1 to 20 before treatment; to 1 to 2560 at the end of two months. A bleeding was made on November 4, 1926. The serum obtained was preserved for therapeutic trial. This has been the serum used in the treatment of the patients herein reported, with the exception of Patient I, as already indicated. This animal was then placed on intravenous injections of live organisms, and with increasing doses the serum agglutinin titer has risen rapidly. The immunization of the horse was begun on August 30, 1926, and the process is being continued at present (December 10, 1926). It is noteworthy that the serum used in the treatment of patients reported at this time was obtained from the horse after only two months of immunization with cultures killed by heating to 60° C. for one hour.

We are presenting below a series of 9 cases, treated with this therapeutic serum. We realize the inadequacy of such a short series in support of definite conclusions in regard to the absolute specificity of this serum.

In addition to the use of the serum, vaccines prepared from Streptococcus cardioarthritidis have been used in the treatment of a considerable series of cases of subacute and chronic arthritis. While these data have not as yet been collected and analyzed, there has been a striking improvement in a small percentage of the group, definite improvement in a larger number and no improvement in others. We hope to present the details of this work in a future communication.

**Case Histories.** PATIENT I. M. M. Admitted August 5, 1926, to the service of Dr. Schnabel. Discharged October 19, 1926. A white girl, aged thirteen years, states that about six to seven weeks before admission she had an attack of tonsillitis. Two weeks later, her throat had practically cleared up when she developed acute rheumatism starting in the left ankle, which became red and tender. Following this the other ankle became involved and then both knees. After this arthritis had in a measure subsided, she developed "Saint Vitus Dance." This latter symptom dates back two weeks before admission to the hospital.

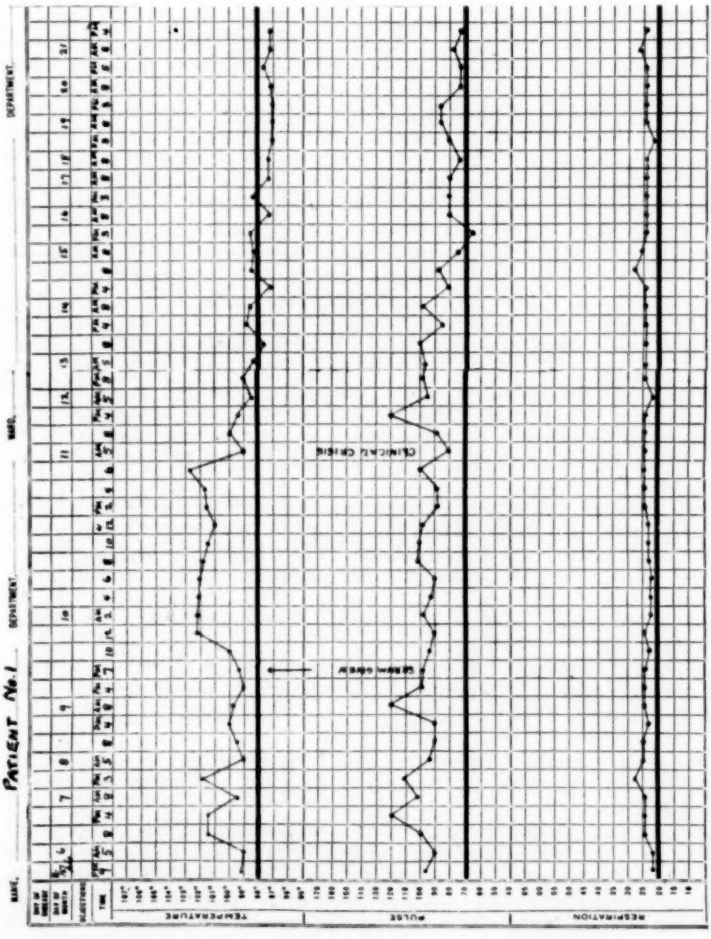


CHART I

*Past Illness.* Patient had diphtheria as a child, also measles and mumps. She has been subject to frequent attacks of tonsillitis.

*Family History.* Her mother has been subject to attacks of rheumatism, her father is a diabetic. Five brothers and sisters, died in infancy; three living, all having had attacks of rheumatism, but none having had chorea.

*Physical Examination.* The patient is large, well-developed, white girl, aged thirteen years, but appearing sixteen years of age. She shows very

pronounced choreiform movements, more pronounced on the right side of the body, than on the left, and most marked in the right arm. Her face is flushed. There are no noteworthy findings in the eyes and nose. The teeth are in good condition. Her tongue is coated and the tonsils are enlarged and cryptic. The chest is symmetrical; breasts are well developed; lungs are resonant throughout, and there are no rales, nor adventitious sounds. The heart: Right border 4 cm. from the midsternal line; left border, 9 cm. The valvular sounds are of good quality, there is a soft systolic murmur, heard all over the precordium and transmitted to the axilla. Her blood pressure is 110/66.

*Abdomen.* No abnormal findings.

*Extremities.* The reflexes are present and very active. There are choreiform movements of the face, lips, arms, legs, most marked on the right side. An urticarial eruption appears on the arms and thighs.

*Diagnosis.* Sydenham's chorea. Mitral valvulitis. Urticaria.

*Treatment.*—The patient was placed in bed, in a screened-off section of the ward, the bed covering elevated and she was given a half grain of luminol every four hours. This was continued until August 9 without any marked effect. At about 7 o'clock on the evening of August 9, she received an intramuscular injection of 20 cc. of antirheumatic rabbit serum. This was followed by a marked febrile reaction, which continued for about thirty-six hours, whereupon there was a decline of temperature by crisis on the morning of August 11. Choreiform movements had lessened by this time so that the patient rested quietly in bed. By August 12, these choreiform movements had ceased, and the patient appeared greatly improved. There was a beginning of return of strength in the right arm which had shown practically a flaccid paralysis. This patient was observed in the hospital for more than two months. Before discharge from the hospital a tonsillectomy was performed. A follow-up on this patient on November 19 showed her to be in excellent condition. She has had no return of either rheumatism or chorea.

Chart I shows the pulse, temperature and respiration record of this patient prior to and immediately following her treatment with serum.

Urine examinations on August 21, 23, 24 and October 5 were normal.

Blood count, August 7, leukocytes 7600, hemoglobin 11 gm. per 100 cc. of blood.

Electrocardiograph, August 27, normal. Tendency to left ventricular preponderance.

Roentgen ray examination, August 27, lung fields are practically normal.

Teleroentgenogram, left border 7 cm. and right border 3.6 cm. from midsternal line.

PATIENT II. E. M., white male, aged forty-three years, a painter by occupation, was admitted on November 13, 1926, to the service of Dr. Robert G. Torrey.

*History.* The patient complained of swollen and painful joints since October 15. The condition began with sudden sharp pain in left ankle which soon became swollen, red and tender. After three days, the pain and swelling subsided and the left knee became involved in a similar process. Following this the right elbow, left ankle and the metatarsophalangeal joints of the left foot and the metacarpophalangeal joint of the left thumb became involved. The patient thinks he had fever during this period. He had no shortness of breath, cardiac palpitation, precordial pains, nor acid sweats. The patient has had several similar attacks, the last one being February 26, 1926. The initial attack of rheumatism occurred in 1919. The patient had been in the hospital on several occasions, prior to this admission. His condition was each time diagnosed rheumatic fever.

*Physical Examination.* The left knee joint is tender, but not hot. There is considerable swelling together with signs of fluid in the bursa. The right ankle is hot, tender and swollen. The left ankle is painful. The left metatarsophalangeal joints are red, swollen and tender. The right

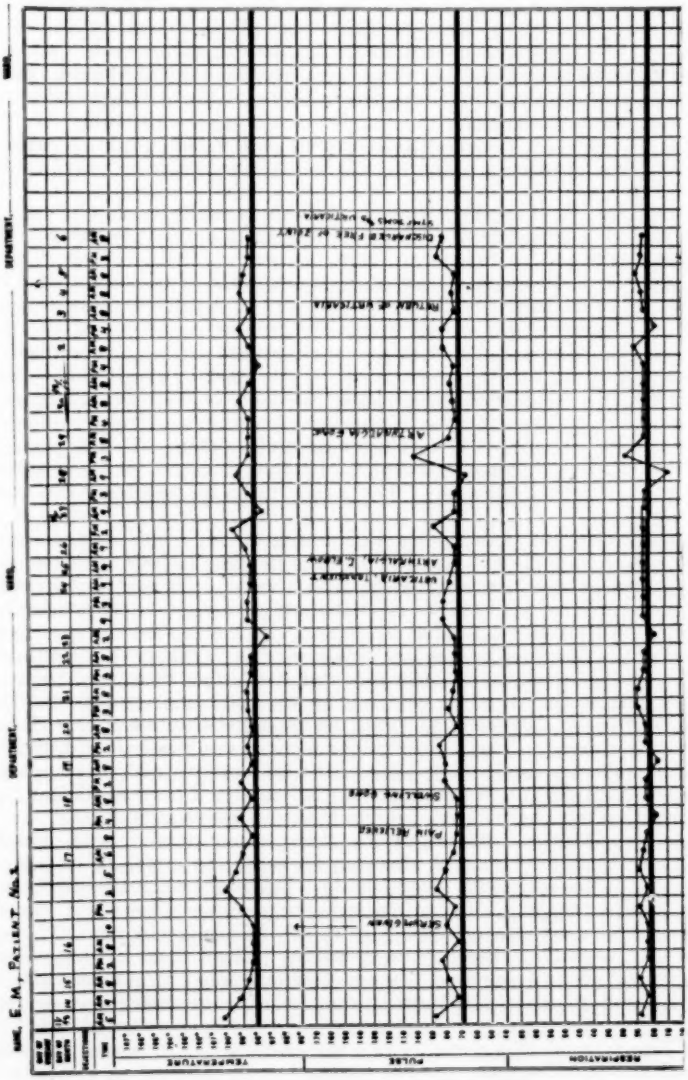

CHART II

elbow shows limitation of movement and pain upon manipulation. The tongue is clean, teeth in good repair, no pyorrhea. The tonsils have been removed. The throat is injected. There is no cervical adenopathy. The chest is clear and resonant throughout. The cardiac dullness is not en-

larged and there is no precordial pulsation apparent. The heart sounds are of good quality. There are no murmurs.

*Diagnosis.* Acute exacerbation of rheumatic fever, with fluid in left knee joint.

Blood count on November 16, 1926, showed erythrocytes 3,450,000; hemoglobin 10.6 gm. per 100 cc. of blood; leukocytes, 7200; polymorphonuclears, 78 per cent; eosinophiles, 2 per cent. At 10.30 A.M. on November 16, 28 cc. of antirheumatic serum was injected intramuscularly. During the next twelve hours, slight headache, general malaise and a slight exacerbation of pain in the joints was experienced. A slight temperature rise accompanied these symptoms. On the morning of November 17, the patient was relieved of pain and tenderness in the joints. Some swelling of the left knee remained. This in turn had disappeared in another twenty-four hours.

*Note by Dr. Torry on November 15.* "There is slight emphysema of the chest and some bronchitis. The heart dullness is normal in extent. The apex beat does not indicate largeness of the heart. The heart tones are of fair quality. Both second sounds at the base are slightly accentuated. No definite murmur appears. There is a history of recurrent arthritis since 1919 affecting the feet, ankles, knees, both elbows, both wrists and the finger joints. The attacks have been symmetrical. There is considerable degree of flatfoot. A scar from an old injury appears over the left knee.

The feet are swollen, red, tender, particularly below the internal malleolus on either side. The left knee is considerably swollen. There is effusion in this joint. The right elbow is tender and swollen. This appears to be a case of recurrent rheumatic fever, with the primary attack seven years ago and frequent attacks since. The patient had a tonsillectomy two years ago."

November 16, the patient slept well during the night and was comparatively free from pain next morning for the first time in four or five weeks. He feels perfectly well, except for a slight headache. There is slight tenderness below internal malleolus of right foot, otherwise joints are not tender. There is free movement in all of the joints. He states that the movement of the right foot has not been so free for three years. This patient continued pain free until the ninth day after receiving the serum when he complained of sharp pain in the left elbow, which joint was also tender, swollen and red. On the eighth day following the serum, an urticarial eruption appeared over the back and chest. This painful joint remained practically unchanged for several days, when improvement began and by November 29, all symptoms referable to this joint had disappeared. At this time it became evident that the condition was that of an arthralgia resulting from serum disease.

*Laboratory Studies.* November 15, urine, straw-colored, acid, specific gravity 1.016, heavy trace of albumin, no sugar, no casts, an occasional leukocyte. November 16, blood count: Erythrocytes, 3,450,000; leukocytes, 7200; hemoglobin, 10.6 gm.; polymorphonuclears, 78 per cent; lymphocytes, 18 per cent; eosinophiles, 2 per cent. November 15, blood Wassermann test, negative. Blood culture, sterile. Blood sugar, 93 mg.; blood urea, 38 mg.; blood uric acid, 3.8 gm. and creatinin, 1.5 mg. per 100 cc. November 22, the electrocardiograph showed left ventricular preponderance only.

On December 3, this patient had a return attack of urticaria, this time without any joint symptoms. The patient left the hospital on December 6 in excellent condition.

PATIENT NO. III. W. H. L., a white man, aged fifty-five years, laborer, was admitted to the service of Dr. Boston on November 15, 1926. He had been ill for seven weeks with cough, soreness within his chest, and rheuma-

tism affecting both lower extremities from the knees downward. His family history was negative. The patient had had pneumonia ten years ago; gonorrhea, two or three attacks, and a chancre thirty-seven years ago. There was no history of a previous attack of rheumatism. The patient noted swelling of the ankles at night after being upon his feet all day. This swelling disappeared during the night. He had been under treatment for five weeks for this condition. Pain from knees to ankles had been present for three weeks. This pain was of a dull aching character and was more or less continuous. He has had pain also in the frontal region of the head, and pain in both arms for the past two days only. The pain in the arms is similar to that in his legs. In the right arm it extends from the shoulder to finger tips; in the left arm, from the elbow downward only. He has also noticed transitory puffiness of the hand and numbness. The cough has been nonproductive and of moderate severity for the past two weeks. He has had no chill nor fever, but has had night sweats occasionally for the past three weeks. He has been a moderately heavy drinker.

*Physical Examination.* The patient is an adult white man, aged fifty-five years, who appears much younger. He is somewhat verbose, but answers questions intelligently. The eyes, ears and nose are negative. The mouth shows extensive gingivitis, extensive pyorrhea with the tongue slightly coated and the pharynx red and dry. Bilateral cervical adenitis is present. The chest is emphysematous and expansion limited. Resonance is impaired over both apices with many crepitant rales over both bases posteriorly and the breath sounds diminished over the right base. The heart dullness is not increased; the sounds are distant and there is a soft systolic murmur over the apex. The blood pressure is 100/48. The abdomen is negative.

*Extremities.* There is tenderness upon pressure over the forearms, over the metacarpal bones and over the calf of the leg. Both lower extremities are edematous about the ankles and over the dorsum of the feet.

*Tentative Diagnosis.* Acute rheumatic fever. Acute bronchitis and a functional systolic cardiac murmur.

*Treatment.* This patient received two injections of antirheumatic serum, the first on November 16, and the second on November 18, without benefit so far as pain and local manifestation in the extremities were concerned. On November 23, the patient was examined by both Drs. Riesman and Boston. Dr. Riesman's note states that there is a little swelling over the dorsum of the feet and ankles, no swelling of the knees, but tenderness over middle of the thigh. There is an impairment over the base of the right lung, posteriorly, with numerous rales underneath, and increased voice sounds. There is suggestive bronchial breathing. Note by Dr. Boston: There is edema along tendon of Achilles about the ankle and over the dorsum of the left foot and slight edema of the right foot. The edema of the left foot extends about 2 inches over the ankle. There is tenderness over the knee joints, especially over the patella. There is no tenderness over the tibiofibular articulation. There is no evidence of an acute cardiac condition.

On November 30, physical examination revealed more definite signs of a pulmonary lesion at the right base. Roentgen ray examination on November 22, revealed a slight haziness over the left frontal sinus, suggesting a diagnosis of frontal sinusitis. Roentgen ray examination of the ankle joints on November 26 showed a rarefaction over the upper and outer portions of the os calcis. The cuboid seemed somewhat rarefied and also the inferior and anterio-inferior portions of the astragalus. This appearance is not seen in the right foot. Roentgen ray examination of the lungs on November 27 showed a large and fairly well defined oval shaped shadow at the right base. Fluoroscopically no pulsation was demonstrable.

Lateral radiogram of the chest shows that the lesion is situated approximately central within the chest cavity. It is apparently adherent to the diaphragm. The remainder of the lung fields is apparently normal. Roentgen ray examination of the lungs on December 2 showed that the above

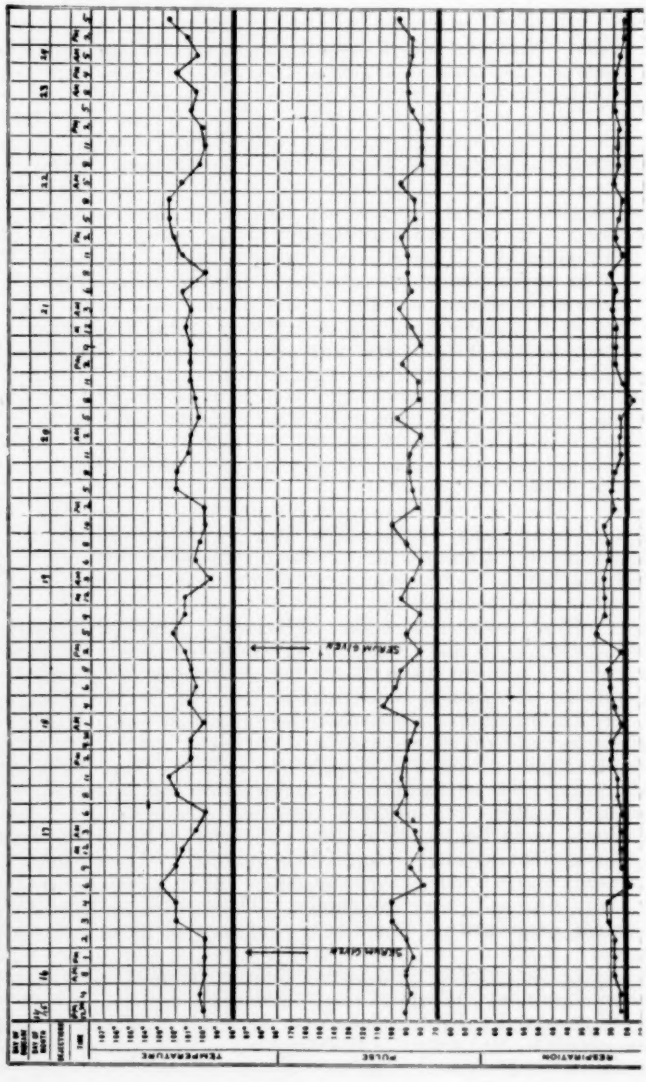

CHART III

findings had remained unchanged. On November 22, a throat smear showed Vincent's angina. On November 17 a urine examination gave normal findings. Blood counts, November 19, erythrocytes, 4,220,000; leukocytes, 37,300; hemoglobin, 10.1 gm.; polymorphonuclears, 97 per cent; lymphocytes, 3 per cent. Nobember 26, leukocytes, 47,200; polymorpho-

nuclears, 78 per cent; lymphocytes, 21 per cent; mononuclears and transitionals, 1 per cent. The Wassermann test on November 18 was negative; the blood sugar, 96 gm. and the blood uric acid, 3 gm. per 100 cc. of blood.

*Note.* The more careful study of this patient has demonstrated a frontal sinusitis and a pulmonary lesion (probably an abscess) which have contributed to a toxic osteitis and osteoarthritis. The patient was not a case of acute rheumatic fever, but this record is inserted because the patient received treatment with antirheumatic serum under the mistaken diagnosis and thus serves in a measure as an indirect control for the specificity of this serum.

PATIENT No. IV. A private case of Dr. Edwin Town, Narberth, Pa. Consultant, Dr. David Riesman. Laboratory examination by Dr. John Eiman. J. C., white schoolgirl, aged fourteen years, began about November 14 to have sorethroat and slight cervical adenitis. Examination of the throat at this time showed an acute inflammatory reaction spreading out from the stub of a tonsil which remained after an operation performed a year or so previously. After several days this condition subsided but a bulging of the pharyngeal wall back of the posterior pillar was noted. In three days this abscess ruptured spontaneously. The local process improved, but rheumatism started, first in right hip, then in both knees and ankles, and lastly in small joints of fingers. The temperature ranged between 100° and 102° F. After two days more the temperature record as shown in Chart IV was begun.

*Physical Examination.* November 26. The patient is a large, well-developed white girl, appearing acutely ill. She lies quietly in bed. The joints involved at present are the right knee and ankle, the left ankle and the small joints of both hands. These joints are swollen and the skin over them is red and excessively warm. Upon movement or upon gentle palpation marked pain is elicited. A throat culture showed Streptococcus cardioarthritidis. Culture of the patient's blood remained sterile. The patient's serum failed to agglutinate the specific streptococcus.

*Treatment.* The patient had received moderate doses of salicylates from the onset of her joint symptoms until November 26, when serum was administered. The serum was injected intramuscularly at 7 P.M. on November 26. The following morning the fever had subsided and the joint pains were relieved. The following day the joint pains had disappeared. At this time, also, the local swelling had disappeared with the exception of one small joint in the finger which remained slightly swollen, and somewhat tender. In another twenty-four hours this local manifestation had also disappeared. A follow-up on this patient on December 8 showed her condition to be entirely satisfactory. A transient urticaria had appeared on December 2 but no arthralgia accompanied it.

PATIENT V. Mrs. F. B. A white woman, aged twenty-eight years, was admitted to University Hospital service of Dr. Alfred Stengel on November 25, 1926. The patient was well until six days before admission, November 19, when she noticed some soreness of her throat which lasted about three days. On November 22, at 9 A.M., she was taken sick with pain and swelling in the right hip, right shoulder and right knee. There has been no other joint involvements. The patient is married and has two children. She denies venereal infections. She has never had a previous attack of joint trouble. The family history is negative. She has been divorced from her husband.

*Physical Examination.* The patient is a young, adult, white female, who appears to be in great pain. She is well developed and well nourished and the skin has a good color. The left pupil is slightly larger than the right,

but both react to light and accommodation. The right ear drum shows a perforation and the right canal contains some cerumen and pus. There is evidence of infection about the teeth. The tonsils are small and deeply buried. The anterior pillars are slightly reddened. Coagulated blood is

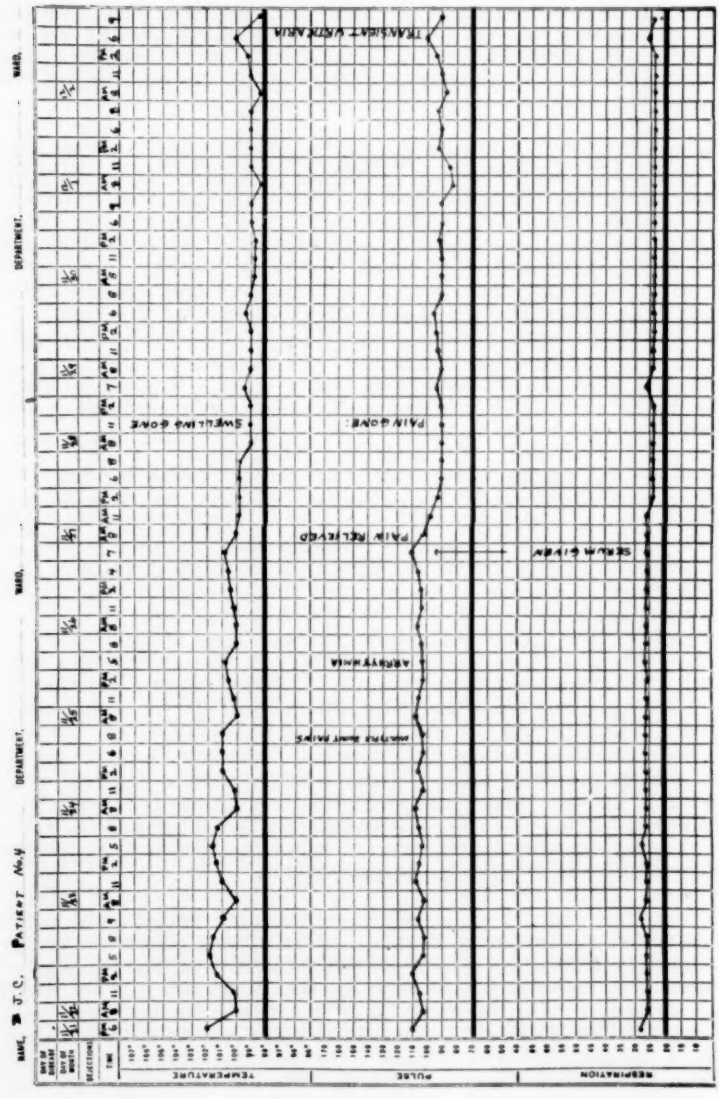


CHART IV

seen in the pharynx, apparently extending down from the nasopharynx. The right sternoclavicular joint is swollen, red, tender and painful. There are no noteworthy findings in either the lungs or the heart. There is no abdominal tenderness nor rigidity. There is marked pain on motion of the

right hip joint, and tenderness over this joint. The right knee is painful when the leg is extended. There is a very slight swelling and some tenderness about this joint.

*Tentative Diagnosis.* Acute rheumatic fever.

November 25, leukocytes, 10,100; November 26, erythrocytes, 3,860,000; leukocytes, 9000; hemoglobin, 71 per cent; polymorphonuclears, 76 per cent; lymphocytes, 21 per cent; mononuclears and transitionals, 3 per cent. Urine, cloudy, specific gravity, 1.025; acid, no sugar, trace of albumin, few granular casts, several erythrocytes. Very many clumped leukocytes. November 27. Urine examination, cloudy; specific gravity, 1.027; acid, no sugar, trace of albumin, occasional hyalin casts, occasional erythrocytes; 16 to 18 leukocytes per high-power microscopic field; many epithelial cells, crystals of uric acid and calcium oxalate. Blood culture remains sterile. Complement-fixation test with gonococcus antigen, strongly positive with 0.15 cc. of the patient's serum. The patient's serum agglutinates antigen of Streptococcus cardioarthritidis up to dilutions of 1 to 40. A throat culture shows Streptococcus cardioarthritidis.

At 6 P.M. the patient was given 30 cc. of antirheumatic serum by intramuscular injection into the left deltoid. All other medication, except opiates for pain, was stopped.

November 28, the pain was unchanged in intensity until 2 P.M., when it entirely disappeared from the joints. At 4.30 P.M. the pain had recurred with diminished intensity in the right hip.

November 29, leukocytes, 15,100. At 5 P.M., on this date, a second injection of 30 cc. of antirheumatic serum was given into the gluteal muscle.

November 30, there was no febrile reaction following the second injection of serum. The pain subsided during the evening, so that she slept quite well without medication. Today she has practically no pain, except when the thigh is extended.

Urine examination: Amber color, cloudy, specific gravity 1.020; acid, trace of albumin, no sugar, no casts, trace of mucus, 1 or 2 erythrocytes and 20 to 22 leukocytes per high-power microscopic field, leukocytes 12,000. Blood Wasserman test, negative.

December 1. The pain and tenderness persists in the right hip and the right sternoclavicular joints. The pain and tenderness of the right knee have almost entirely disappeared. Leukocytes, 12,000. Urine examination: Amber, cloudy, specific gravity 1.015, acid, trace of albumin, no sugar, occasional hyalin casts, few cylindroids, trace of mucus, no erythrocytes; 3 to 4 leukocytes per high-power microscopic field.

December 2, urine examination: Amber, cloudy, specific gravity 1.018, acid, trace of albumin, no sugar, occasional hyalin casts, few cylindroids, trace of mucus, occasional erythrocyte and several leukocytes.

December 3, urine examination: Amber, cloudy, specific gravity 1.018, acid, trace of albumin, no sugar, few hyalin casts, trace of mucus, 1 or 2 erythrocytes and many clumped leukocytes.

December 3, cervical smear: many pus cells. No Gram-negative; intracellular diplococci; many Gram-negative and Gram-positive bacilli; many Gram-positive cocci. Urethral smear: Many pus cells; no Gram-negative intracellular diplococci.

December 5, typhoid vaccine, 20 billions of killed organisms, was given intravenously at 5.30 P.M. In about thirty minutes, the patient had a rather hard chill with a temperature rise to 102.2° F. This chill lasted about fifteen minutes and was followed by profuse sweating.

December 6, leukocytes, 10,300. Urine examination: Straw color, cloudy, specific gravity 1.010, acid, trace of albumin, no casts, no mucus, occasional erythrocyte; 8 to 10 leukocytes per high-power microscopic field.

Otolaryngologic report: Dr. Husick. The patient has a slight infection of left tonsil and because of arthritis they should be removed.

December 7, Roentgen ray examination of right hip joint showed slight destruction of the cartilage of the right hip joint with close approximation.

December 11, Buck's extension was applied to the right leg.

December 12, subcutaneous injection of 150 billions killed organisms of Neisserian vaccine was given at 7.45 P.M.

*Revised Diagnosis.* Gonorrheal arthritis. This patient showed a temporary beneficial effect from the nonspecific reaction following the second injection of the serum. This effect aids in timing the period of euphoria in the foreign protein reaction following the injection of the antirheumatic serum.

PATIENT VI. A. B., a white girl, aged twenty-five years, nurse, was admitted on October 28, 1926, to the hospital service of Dr. Doane. She remains in hospital under treatment to date. This patient entered the hospital complaining of a heavy cold in the chest and cough with scanty expectoration. There appeared occasional rales throughout the chest anteriorly. The heart action was rapid, but regular. There was a faint mitral systolic murmur. On admission her temperature was 100° F.; pulse, 120; and respirations, 24.

This patient had her first attack of rheumatic fever in January, 1926. It began on January 27, with involvement of the hips. There was successive involvement of the knees, ankles, elbows, shoulders, and small joints of the feet and hands. During this attack severe pancarditis developed. She remained in the hospital under treatment until June 15. Between this date and the onset of the present attack, she has been free from arthritis.

Two days after admission on October 30, she complained of pain in the wrists and ankles.

Because of her antecedent history, the diagnosis, an acute exacerbation of rheumatic fever with mitral endocarditis was made. The patient was confined to bed and placed on 10 gr. of sodium salicylate, three times daily. Tincture of digitalis was given in small doses. The sodium salicylate was later discontinued on account of gastric intolerance to the drug. Between the time of admission on October 28 and November 28 the temperature had ranged between 99° and 101.2° F., and the pulse rate between 90 and 120. On the latter date, after a period of almost a week, during which the temperature did not rise above 99.4° F., an acute flare-up of the joint symptoms occurred with a rise in the temperature to 101° F. at 11 A.M. on November 29. At this time 30 cc. of antirheumatic serum was given intramuscularly. There appeared no relief of the joint symptoms during the next twenty-four hours, so that on November 30 a second injection of 30 cc. of the serum was given. This was followed by considerable relief of pain in the joints with the exception of those of the right hand. No reduction of the temperature, however, was observed to follow this injection. On December 2, sharp precordial pains were experienced. An examination revealed a pleural pericardial friction rub. Later a pericardial friction rub alone, was found. At 11 A.M. on December 3, a third intramuscular injection of 30 cc. of serum was given. This was followed by relief of the joint symptoms, pain, swelling and redness, beginning within twelve hours and continuing until December 11 when the arthralgia of serum disease appeared. This continued for three days and disappeared spontaneously. The temperature declined, temporarily beginning about twelve hours after this last injection, but subsequently rose on the fifth day of the month to 104° F. On December 6, a transient urticarial eruption appeared. Several return attacks of the skin eruption appeared between December 6 and December 14. From December 7 to December 10, the temperature had been around 100° F., when on the latter date the temperature rose again and ranged between 102° F. and 104° F. during the next five days. The pericardial pain necessitated the use of a narcotic.

Blood counts: December 11, leukocytes, 15,500; December 12, 5400; December 13, 5400; December 14, 5500; December 16, 11,600. Blood culture: December 11, sterile.

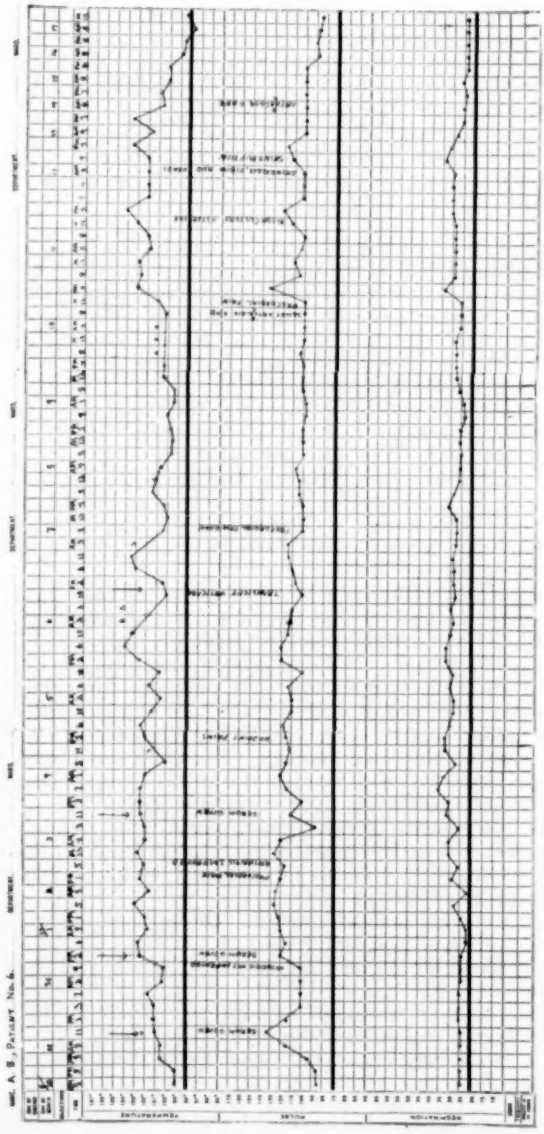

CHART V

December 16 the temperature declined to 99° F. and continued at the normal level up to the last included observation at noon on December 17. There has been no joint pain since the disappearance of the serum arthralgia. All of the joints are now freely movable and quite painless.

This patient received in all 90 cc. of the antirheumatic serum in divided doses. The arthritis was controlled only after the third injection. Before the temperature had returned to normal following the third injection, the effects of serum disease arose to complicate the clinical picture. In the temperature chart sharp rises are noted to follow at six days after both the first and the second injections of serum, and a prolonged period of serum sickness followed the third, at an interval of seven days. The blood counts and the presence of the skin eruptions are the indications that this latest period of hyperpyrexia was that of serum disease.

It is unfortunate that later observations cannot be included, since this has been by far the most interesting case of the group reported. Obviously the verification of the above analysis must depend upon observation of her subsequent course.

PATIENT VII. E. G. A white boy, aged ten years, was admitted to the service of Dr. Francis O'Neill at St. Agnes Hospital on November 27, 1926. His present illness began in October with extreme restlessness and choreiform twitchings. These affected all four extremities. He was unable to feed himself without spilling food and drink. He attended the children's clinic, but was unable to be controlled and was consequently sent to the hospital for observation and treatment.

The boy had had the first attack of chorea at the age of seven years and was treated in the Methodist Hospital at that time. His tonsils were removed before discharge from the Methodist Hospital. He has had measles, mumps and chickenpox. He was treated in the St. Agnes Hospital in July, 1926, for a fractured hip. He showed no choreiform movements at this time. His mother is dead of an undetermined cause. His father, one brother and two sisters are living and well. Three sisters are dead of unknown causes.

*Physical Examination.* The child is very restless but answers questions intelligently. There are well-marked choreiform movements of arms, legs, head, and so forth. Examination of head is essentially negative. The teeth and gums are in good condition. There is present a bilateral cervical lymphadenophy. The chest is symmetrical and resonant throughout. The heart shows no increased area of dullness, a regular rhythm with valvular sounds of good quality and no murmurs. The remainder of the physical examination reveals no abnormal findings. The child was placed in bed, the bowels opened freely with a saline cathartic and at 3 P.M. on December 1, 30 cc. of antirheumatic serum was given intramuscularly.

December 2. Movements of right forearm and wrist and left side of face are still present but patient appears remarkably quite generally. He did not spill any water when drinking this morning, an impossible accomplishment before serum was given.

December 4. The child is much quieter. He can feed himself without any difficulty or spilling of food and drink.

December 6. The child is much improved. There is still some slight twitching of the shoulders.

December 8. The child continues to improve. There is still a slight twitching of shoulders. No other abnormal physical signs.

December 11. Only very occasional twitching of shoulders seen. The patient is quiet.

December 15. No twitching observed. The child is up and about the ward and has no complaints.

November 29. Urine examination, negative.

PATIENT VIII. A. R., a white, married woman, aged twenty-four years, a private patient of Dr. Louis M. Golden. The onset, November 26, followed a traumatic injury of the left ankle which was diagnosed as a sprained ankle of moderate severity. Two days after the injury the patient

developed a sore throat and general malaise. Following this, the right ankle, left wrist, left shoulder and the right thumb became involved and showed the signs of an acute arthritis. December 3, the patient was seen with Dr. Golden. She was confined to bed with pain and swelling of both ankles, pain in the left shoulder, and pain and swelling of the metacarpophalangeal joint of the right thumb. The temperature was 100.2° F., and the pulse 112. The patient is a rather obese young woman who appears to be in considerable pain. The skin is moist and pallid. The throat is inflamed about the anterior pillars. There is no cervical adenopathy. The lung areas are clear. The heart sounds are of good quality, the rhythm regular, and no murmurs are heard.

The patient had been receiving salicylates with benefit up until this date, December 3. At 4.30 P.M. on this date 30 cc. of antihreumatic serum was injected into the gluteal muscles. During the next thirty-six hours the temperature ranged from 99.2° F. to 100.2° F., and the pulse from 100 to 110. On December 5 the temperature declined to 98.4° F. and the pulse to 96. All the joint pains were better and the local indications about the joint subsiding. December 6 the condition was improved; the temperature range from 99.4° F. to 100° F. December 7, at 11 A.M. the temperature was 98.4° F. and the pulse 84. All joints are greatly improved. The left shoulder has entirely clear up, and both ankles are much improved. Some swelling in the left wrist is still apparent.

From December 10 to December 15 there appeared a rise of the temperature again with a range from 99° F. to 101° F. There was no skin rash but some pain returned in the left wrist.

December 16 some stiffness remained in the left wrist, but the swelling had disappeared. The temperature in the evening was 99.4° F.

NOTE: It is difficult to evaluate properly the effects of the serum in this case, since she was not under close personal observation. Improvement following the serum injection appears, but it does not seem to be complete enough to make the claim of complete detoxication. This brings up the question as to whether the dosage administered had been sufficient. Beginning one week after the injection there appeared a rise of temperature and some return of pain to the wrist joint. This occurred within the period during which in adults we have come to look for arthralgia of the late serum reaction.

PATIENT IX. H. L., a white boy, aged five years, was admitted to the service of Dr. Le Boutillier, Children's Department, Philadelphia General Hospital, on December 5. Discharged, December 15. The patient complained of pains in the knees and ankles. The condition began on November 30 with fever, chills and anorexia. Arthritis began in the knees and on December 4 the ankles became involved. There had been no previous attack of a similar nature.

*Physical Examination.* A rather anemic-looking white boy sits in bed with the knees flexed, and cries considerably from pain. His face is pallid, with dark circles under the eyes and he looks very ill. The outstanding physical findings are that the tonsils are enlarged and cryptic; the anterior pharyngeal pillars are moderately reddened; but there is no cervical adenopathy. The chest is fairly well developed. There is good resonance throughout. No rales are heard. The heart is very irregular and a soft systolic murmur appears at the apex area. There is present a skin eruption which suggests scabies. Both knees are extremely tender upon palpation. The right knee is swollen, the skin over it warm, but there is no especial redness of the skin about it. Neither leg can be extended because of the excruciating pain in the knees. Both ankles are painful upon motion, but do not appear to be swollen, nor is the skin over them reddened.

*Diagnosis.* Acute articular rheumatism, hypertrophied tonsils, endocarditis and scabies.

*Treatment.* Upon admission 1 cc. of triple distilled water was injected intravenously, without apparently affecting the pain. At 12.30 P.M., December 6, 30 cc. of antirheumatic serum was given intramuscularly. The child had slept very little since admission, crying almost constantly because of the pain. At 3 P.M. the child fell asleep and awakening at 4 P.M. said the pain in the legs was much better.

December 7. The child seemed comfortable today and did not complain of pain. The right knee had decreased in circumference from $10\frac{1}{4}$ inches, before the injection of serum, to $9\frac{3}{4}$ inches forty-eight hours after the serum had been given. Left knee measured $9\frac{3}{4}$ inches on both occasions.

December 8. The child was able to extend both legs for the first time. He does not complain of pain, nor is any tenderness noted upon palpating the affected joints.

December 6. Urine examination gave normal findings. This patient had no medication except a saline cathartic, upon admission and applications of methyl salicylate to the knees.

December 15. The patient has continued in excellent condition with normal temperature, no pain, and all joints normal as far as could be determined. He was discharged on this date.

**Discussion.** Nine patients have been treated by means of an antiserum, prepared from a strain of streptococcus isolated from the blood of a patient with rheumatic fever. Two of the patients chosen were selected as cases of rheumatic fever, but from further study it appeared that the correct diagnosis was other than rheumatic fever. In these no improvement followed the use of the serum. In all the remaining patients a very prompt improvement followed the injection of the serum in sufficient dosage. The only question which arises hinges about the response of acute rheumatic fever to the nonspecific foreign-protein reaction. This requires careful control experiments on our part, made upon patients showing stages of rheumatic fever, comparable to those reported, and treated with corresponding amounts of normal horse serum which is of an age approximately that of the serum used in these patients. Time has not permitted the employment of such a serum in a series of control patients, but these tests are now under way. We have relied upon past personal experience with the response of rheumatic fever to foreign-protein shock as well as that of others as it appears in the literature. We have seen very definite points of difference in the manner of response to the antirheumatic serum and that to foreign protein. We believe that the beneficial effect afforded by the serum used here is the result of a specific action in neutralizing the toxins arising from the infection in rheumatic-fever patients. Our reasons for this are: The beneficial action following intramuscular injection of the specific serum is very prompt and occurs in some instances simultaneously with a decline in temperature (Patients VII and IX).

The effect has been constant and, as far as one can judge at this early date, is of a more permanent nature than that which ordinarily results from foreign-protein-shock treatment (Patients I and II). The detoxication of the patient is readily observed upon clinical observation and parallels the decline of the manifest subjective symptoms, pain in arthritis or the objective symptom, choreiform

movement in the patient with chorea. This whole process is more gradual in its culmination that the sudden relief noted at the beginning of the period of euphoria in patients responding favorably to foreign-protein treatment, so that the relief of subjective or objective symptoms is not complete at a time when this period of euphoria should begin following intramuscular injection of such a protein as horse serum. This detoxication (Patient VI) appears to depend upon adequate dosage of the antitoxin. In Patient VI a grave rheumatic infection cannot be doubted. The first injection (30 cc.) aggravated the subjective symptoms; the second injection (30 cc.) was followed by an appreciable decline of pain, swelling and stiffness of the joints involved, which was accompanied by pleuropericardial pain, perhaps because of the adsorption of fluid exudates separating these inflamed serous surfaces from the same mechanism which mobilized the joint exudates; the third injection (30 cc.) terminated the arthritic symptoms, and was followed by improvement in the heart action after spontaneous disappearance of the friction pains.

From the theoretical standpoint, the serum, because of its manner of preparation, should possess both bactericidal and antitoxic properties. Its action upon trial, however, suggests that the antitoxic property is responsible for the results obtained. In Patient II a throat culture was made six days after the injection of the serum still yielded a positive growth of Streptococcus cardioarthritidis.

We believe, therefore, that the serum acts chiefly through its content of antitoxin, and that its specific action in rheumatic fever, should further experience support the favorable results to date, is an indisputable proof that the microörganism, Streptococcus cardioarthritidis, from which the serum was made, is the specific bacterium causing rheumatic fever and its various allied and complicating conditions, chorea, endocarditis, myocarditis, pericarditis, pleuritis, tonsillitis, pharyngitis, etc.

Although Koch's postulates have not been fulfilled for this microorganism, it might be noted that they have never been fulfilled in several instances, where for a number of years the microörganism has been generally accepted as the cause of a disease. We have no doubt but that they may be fulfilled in this instance. Our greatest concern has been that of developing a specific serum to be applied in relieving human suffering. We further believe that a specific beneficial effect of a therapeutic antiserum constitutes the strongest possible proof of the causative relationship to a particular disease of the microörganism used in its production.

**Theoretical Considerations.** One cannot begin at this time to appreciate the benefit which is likely to arise from a specific treatment of rheumatic fever. Its greatest field naturally lies in its application early in the first attack of the disease, especially in children. It is in this manner that greatest hope for *preventing heart disease arises*. With established heart disease (especially myocardial and pericardial) the hope arises for the speedy termination

of its progressiveness and its beginning healing. Even with mechanically damaged hearts, it is reasonable to hope that the removal of the toxic element (which the persistence of Aschoff bodies indicates as continuing long after tangible signs of infection have disappeared) will permit the more efficient functioning of the tissues which remain. For chorea it appears that an abrupt termination of the condition can be effected. What may be its application in chronic arthritis, that great and inadequately classified group? May it not enable one to pick out a considerable subgroup caused by the toxins of Streptococcus cardioarthritidis and terminate such cases by the use of the antitoxin, or by the antitoxin followed by vaccines? May it not enlighten us, indeed, upon such conditions as chronic nephritis, arteriosclerosis, various anemias, or even upon some of the so-called metabolic diseases? The identification of the microörganism causing rheumatic fever will enable the collection of more complete knowledge in regard its prevalence, its mode of transmission, its localizations in the patient, the pathogenesis of the disease, etc. With the organism in our hands, the whole subject of the experimental pathology produced by it becomes only a matter of time and industry. Its identification with a little studied group of streptococci, presumably of rather low virulence and of widespread distribution, will direct interest toward this group, prompting work which may be fruitful in clearing up etiologic questions in connection with other important chronic and slowly progressive diseases. Can a real test for susceptibility to the infection with Streptococcus cardioarthritidis be developed? What may be done by way of specific immunization against such susceptibility to infection?

These and many more problems suggest themselves. Work on a number of these phases has already been begun, or planned. It is hoped that other investigators may see fit to contribute their thought and effort to the study of rheumatic fever.

**Summary and Conclusions.** A serologically specific nonhemolytic streptococcus with distinctive biologic characters has been isolated from blood and throat cultures of patients with rheumatic fever, or its related conditions, and from cultures of feces in a few patients with chronic arthritis.

The characters of this microörganism have been described. Inoculated into rabbits it has been shown to produce acute arthritis comparable to that of rheumatic fever in humans and a proliferative osteoarthritis comparable to a type of chronic arthritis in humans. The acute illness in rabbits is attended by marked tenderness, redness and swelling of the joints involved, by profound asthenia and atrophy of skeletal muscles, by central nervous system involvement, producing extreme excitability of the animal and pronounced choreiform movements, nodding spasms and flaccidity of one or more of the legs. The infection appears to persist in subacute and chronic stages when animals survive the acute attack of disease.

From the pathologic studies it appears that infection of joint structures, acute degeneration of cardiac and skeletal muscles, formations of small abscesses in liver, lungs, heart and skeletal muscles are the outstanding lesions of the acute involvement following overwhelming doses of the infecting agent. In the subacute stages of this infection the infiltration of large mononuclear cells in interstices between the heart muscle fibers and the formation of the more typical Aschoff-like nodules in the myocardium appear as outstanding findings, especially since the latter is regarded as pathognomonic of rheumatic fever. No opportunity has offered itself to study the brain and spinal cord lesions in animals showing the manifestations of this involvement.

Vaccines of the organism have been used with benefit in a certain number of patients with subacute cardioarthritis or with chronic arthritis. They have failed to produce benefit in other instances of these conditions.

With a newly isolated species of streptococcus, a therapeutic antitoxic serum has been prepared, first in the rabbit and then in the horse. The administration of this serum in proper dosage to patients with rheumatic fever has been followed in a very striking manner by improvement of the outstanding clinical symptoms, pain, tenderness, swelling and stiffness of the joints.

We, therefore, have named this microörganism, Streptococcus cardioarthritidis, and offer it upon the basis of these observations as the cause of rheumatic fever.

My thanks are due to the various physicians mentioned in the text of the case reports for the permission to use the clinical data in this report, and to these, as well as to various members of the resident staff of the Philadelphia General Hospital, for their coöperation in the clinical trials of the antirheumatic serum. For kindly suggestions and material aid in furthering this work, my appreciation is expressed to Drs. E. B. Krumbhaar and J. C. Doane, of the Philadelphia General Hospital. Dr. Krumbhaar has very kindly facilitated the prompt publication of this report. My assistants, Dr. W. A. Kreidler, Mr. R. E. Otten, Mrs. Mary J. Evans, Miss Claire Stam and Miss Justina O'Loughlin, I thank for their many material manifestations of loyalty, faith and interest in this work.

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# REVIEWS.

FUNDAMENTALS OF DERMATOLOGY. By ALFRED SCHALEK, M.D., Professor of Dermatology and Syphilology, University of Nebraska College of Medicine; formerly Assistant Professor of Dermatology, Rush Medical College; Member of the American Dermatological Association; Chief of the Dermatological Service, Nebraska University Hospital; Dermatologist to the Methodist Episcopal, the Immanuel Hospitals, etc. Pp. 239; 54 illustrations. Philadelphia and New York: Lea & Febiger, 1926. Price, $3.00.

THERE is a distinct need for a book somewhat larger than a compend but not so bulky as a treatise.

Schalek has compiled an excellent small volume with a few but satisfactory photographs.

The arrangement of skin eruptions, always somewhat puzzling, has been placed on an alphabetical basis.

Under the heading of "dermatological aphorisms," the writer has emphasized a few extremely important points as to diagnosis and line of procedure.

The suggestion might be made that greater elaboration should be given to the arsenical treatment of syphilis.

The common diseases of the skin have all been discussed, and a few lines are given to many of the rarer affections.

F. K.

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NONSURGICAL TREATMENT OF DISEASES OF THE MOUTH, THROAT, NOSE, EAR AND EYE. By THOMAS HELM ODENEAL, M.D. Pp. 428. Philadelphia: P. Blakiston's Son & Co., 1926.

THIS book on the diagnosis and treatment of the mouth, nose, throat, ear and eye is timely for use among general practitioners. Specialists will find little to interest them, as surgery of the parts is practically left out. The chapters on the endocrine glands, focal infection and Roentgen rays are well written and will make interesting reading.

The portion devoted to the treatment of the diseases of the eye contains many statements with which it is felt many opthalmologists

will disagree, especially the chapter on refraction and muscular errors. Although it is not meant to be an exhaustive work, most of the recent methods of treatment are duly discussed. D. H.

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EARS AND THE MAN. By ANNETTA W. PECK, ESTELLE E. SAMUELSON and ANN LEHMAN, of the New York League for the Hard of Hearing. Pp. 217. Philadelphia: F. A. Davis Company, 1926. Price, $2.00.

THIS book is a clear and concise presentation of the problem facing the deaf or deafened individual in their effort to adjust to the business of living. We are then led through a logical consideration of hearing in its relation to mental processes, the sharpening of the senses and the normal self expression of the personality of the individual. Next in order are definite suggestions for the meeting and overcoming of the handicap through medical attention, lip reading and mechanical hearing devices. Last, definite instances illustrate side by side successful and unsuccessful attempts at rehabilitation.

To the social workers in other fields this excellent little book opens up an understanding source of help for clients or patients too often disregarded. Notwithstanding the finality of the tone of the statements, it will also serve as the point of departure for more general intelligent and appreciative discussion of the problem of the deaf or deafened individual. D. T.

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LIGHT AND HEALTH. By M. LUCKIESH and A. J. PACINI, Research Laboratories of the General Electric Company. Pp. 302; 31 illustrations. Baltimore: Williams & Wilkins Company, 1926. Price, $5.00.

THIS book aims at being a popular handbook on the biologic effects of light and heat. Coming from the General Electric Company, it presumably contains true statements of physical facts, but grave inaccuracies abound in the presentation of biologic data.

One instance may be given. The Pacinian corpuscles are "identified with the thermal sense," said to be "intimately associated with the tactile sense," and psychologic effects of light are referred to on this basis. Though these corpuscles have been known for some seventy-five years, their exact function is still unknown, and any such implication of a connection with two different sensations is quite unwarranted. H. B.

SCOLIOSIS. By SAMUEL KLEINBERG, M.D., F.A.C.S., Assistant Surgeon, New York Hospital for Ruptured and Crippled. Pp. 311; 140 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $6.00.

THE author has presented a complete, careful and well-balanced discussion of scoliosis, well worth study by student and practitioner. He properly emphasizes the tremendous importance of the recognition of this deformity in its early stages, while it may be cured or its progress stayed, and advocates the routine thorough examination of all children of public-school age. A severe scoliosis is a terrible handicap to an individual in his physical, social, economical, mental and psychical life.

The chapters on pathology, etiology, prophylaxis and treatment are quite complete and illuminating. The text is very fully illustrated, largely with original photographs. A. G.

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SIXTY YEARS IN MEDICAL HARNESS. By CHARLES BENEULYN JOHNSON, M.D. Pp. 345; 16 illustrations. New York: Medical Life Press, 1926. Price, $3.00.

THIS is the first of the Medical Life Press' Library of Medical History. Five more are in various stages of completion. It is a "placid and prolix" story of sixty years of general practice that serves as a record of this rapidly changing, perhaps vanishing, type during the period of the greatest change in medicine that the world has ever known. The chapters, "Medicine in 1868" and "In the Sixties and Seventies" are of more general interest, though perhaps not of such value as an original record. E. K.

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FACTS ON THE HEART. By RICHARD C. CABOT, M.D., Professor of Medicine and Social Ethics, Harvard University. Pp. 781; 163 illustrations. Philadelphia and London: W. B. Saunders Company, 1926. Cloth, $7.50 net.

THIS is a critical survey of 1906 necropsied cases, covering all the cardiovascular material in the 4000 necropsies done at the Massachusetts General Hospital between 1896 and 1919. Starting from the postmortem diagnoses, the author has worked back into the clinical records corresponding.

The book will appeal particularly to the pathologically trained clinician. For the medical man who has failed to keep his morgue appointments, nearly every chapter contains a number of surprises.

Almost immediately he is greeted with the statement that most "heart disease" is imaginary. Again, that mitral regurgitation is one of the rarest of valve lesions and cannot with any certainty be recognized in life. The proof is "7 cases of that great rarity—mitral regurgitation—" in 1846 necropsied cases of heart disease. In the same series were 107 cases of mitral stenosis.

The discussion of the etiology of pure aortic (valvular) disease as probably due to a peculiar subtype of endocarditis belonging under the rheumatic group will prove interesting to those who have long considered this lesion to be chiefly of arteriosclerotic origin. Contrary to general medical opinion also is his statement that the hearts of athletes are no larger than the hearts of sedentary people. The classification of acute and subacute endocarditis is purely pathologic, and some objection is raised to the term "subacute bacterial endocarditis," which recently has gained wide usage. Acute endocarditis was found to be a complication of acute pericarditis in only 8 per cent of 186 cases. Chronic pericarditis with mediastinitis gives the largest hearts and, in speaking of such large hearts, the author recommends cautious interpretation of apical or left parasternal murmurs, whatever their time.

The book is the work of a great individualist, written dogmatically, but based upon facts. It constitutes a valuable research in a subject that many present-day "functionally-trained" clinicians have mistakenly considered as exhausted, namely, morbid anatomy, and adds considerably to our knowledge of cardiovascular disease. E. W.

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# BOOKS RECEIVED.

*Researches on Hookworm in China.* By W. W. Cort, J. B. Grant, N. R. Stoll and other collaborators. No. 7, Monographic Series, American Journal of Hygiene. Pp. 398. Baltimore: American Journal of Hygiene, 1926.

*Recent Advances in Physiology.* By C. Lovatt Evans, D.Sc. (Lond.), M.R.C.S., L.R.C.P., F.R.S. Second edition. Pp. 370; 70 illustrations. Philadelphia: P. Blakiston's Sons & Co., 1926. Price, $3.50. A quick re-issue confirming the value of this work.

*Reminiscences.* By George Henry Fox, A.M., M.D. Pp. 248; 20 illustrations. New York: Medical Life Press, 1926. Price, $3.50. Personal reminiscences of a long and busy career, student days at the University of Pennsylvania, Blockley, Berlin, Vienna and Paris and medical conditions in New York in the '70s and '80s make pleasant light reading.

*The Heart.* By ALEXANDER GEORGE GIBSON, F.R.C.P. (LOND.). Pp. 108; 15 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $1.50.

*Textbook of Embryology.* By HARVEY ERNEST JORDAN, A.M., PH.D., and JAMES ERNEST KINDRED, M.A., PH.D. Pp. 613; 504 illustrations. New York: D. Appleton & Co., 1926.

*Sulfur Metabolism. A Review of the Literature.* By MAX KAHN, M.A., M.D., PH.D., and FREDERIC G. GOODRIDGE, M.D., PH.D. Pp. 831. Philadelphia: Lea & Febiger, 1926.

*Principles and Practice of Chemotherapy with Special Reference to the Specific and General Treatment of Syphilis.* By JOHN A. KOLMER, M.D., D.P.H. Pp. 1106; 82 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $12.00.

*Principles of Diagnosis and Treatment in Heart Affections.* By SIR JAMES MAKENZIE. Third edition. Pp. 242; 37 illustrations. New York: Oxford University Press, American Branch, 1926 Price, $3.50.

*General Index Volume of the Mayo Clinic Papers,* 1884–1925 *inclusive.* Pp. 227. Philadelphia: W. B. Saunders Company, 1926. Price, $5.00. An extremely good aid to those who have been helped by the publications of the Mayo Clinic. References to articles on the spleen, for instance, fill almost four columns. The last thirteen pages of supplement should not be overlooked.

*The Medical Department of the U. S. Army in the World War. Vol. VI. Sanitation.* Pp. 1141; 148 illustrations. Washington: Government Printing Office, 1926.

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*The Scientific Basis of Chemotherapy. Part I.* By IWAN I. OSTROMISLENSKY, PH.D., M.D. Pp. 142. New York: Inter-American Medical Publishing Company, 1926.

*Principles of Medical Treatment.* By GEORGE CHEEVER SHATTUCK, M.D., A.M. Sixth edition. Pp. 256. Cambridge, Mass.: Harvard University Press, 1926.

*Readings in Abnormal Psychology and Mental Hygiene.* Edited by W. S. TAYLOR. Pp. 789. New York: D. Appleton & Co., 1926.

*Psychoëncephale Studien.* By DR. S. K. THODEN VAN VELZEN. Pp. 190; illustrated. Joachimsthal i. d. Mark., 1926.

*Obesity.* By LEONARD WILLIAMS, M.D. Pp. 171; 20 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $3.35.

# PROGRESS

OF

# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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**An Experimental Study of Chronic Aortic Regurgitation in Dogs.**—BAZETT and SANDS (*J. Clin. Invest.*, 1926, **3**, 65) studied in a large number of animals the changes that occur in the heart and circulation in aortic regurgitation. The study is a very complete one and includes the electrocardiographic records and Roentgen ray measurements. Aside from the physiological aspects of the study, the most interesting deduction from the point of view of the internist is the changed note in the heart size. The authors depend upon the evidence of hypertrophy through measurement by Roentgen ray rather than by the heart-weight-body-weight ratio. They show that the initial changes in the heart values in the first period of one to four months are accompanied by a rapid increase in the heart size. For a period from four months to twelve months the heart still continues to enlarge, but this enlargement is quite gradual. It would be interesting to know just how the application of this to aortic regurgitation in man would be explained by the authors. In man it is difficult to conceive of an aortic regurgitation being anything but a gradual process, which develops most insidiously and most slowly, quite contrary to the acute onset of the valve lesion in experimental studies

**Further Observations on Immunity in Relation to Transplantable Malignant Tumors.**—This last communication of LUMSDEN (*Lancet*, 1926, **211**, 112) reports on a series of animals in whom bilateral sarcomata were produced in each hind foot. In the treated animals the anti-Jensen's rat sarcoma serum was injected in the sarcoma of one side, according to the method which the author employs. In 37 of the

38 treated animals regression began in the untreated foot in about seven to ten days, and went on to complete cure. It would appear from this study that the treatment is not only local but is also systemic in its effect. He also shows that a rat cured of the injection sarcoma is absolutely immune to subsequent inoculations.

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**A Study of the Action of Ammonium Chlorid and Organic Mercury Compounds.**—The popularity of novasurol alone or in combination with ammonium chlorid in the treatment of edema warrants a close study of this work of KEITH and WHELAN (*J. Clin. Invest.*, 1926, **2**, 149) by the many physicians who employ this drug. The present paper shows that the efficiency of these diuretics depends not only upon their activity on the renal cells but also that extrarenal factors enter into consideration. Used in combination, ammonium chlorid and organic mercury compounds will frequently produce diuresis; when alone they fail to do so. The authors say that these drugs cause acidosis, an increase in the chlorid content of the blood and an increase in the excretion of water, chlorid, fixed inorganic base, generally sodium and potassium and ammonia. Diuresis depends upon all these factors. They quote one case in which there was subnormal plasma chlorid and in which the combined drugs failed to produce a diuresis. In other words, the action is not only on the renal cells but also upon the edematous tissue cells throughout the body, permitting chlorid and water to be passed through cells previously impervious, as the peritoneal endothelium in the ascites of cirrhosis of the liver.

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**A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension.**—The William Henry Howell Award for 1926 was won by BORDLEY and BAKER (*Bull. Johns Hopkins Hosp.*, 1926, **39**, 229) for their valuable contribution to the pathogenesis of hypertension. The authors undertook the work under the assumption that there might well be in hypertensive cardiovascular disease a localization of the arteriosclerotic changes in the region of the vasomotor center. These changes, they believed, would produce a lowering of the blood supply to this center and would be followed by compensatory increase in arterial tension. An analysis of their paper would seem to prove that they have carried their point, because in the examination of 24 cases they found that in those brain stems in which there was marked arteriosclerotic change there was also a clinical history of high blood pressure, renal involvement and in some cases cardiac hypertrophy. Whereas, in the majority of cases in which the sclerosis of the vessels of the medulla was slight or negative, the blood pressure was invariably low and there was slight evidence of nephritis. It is pointed out in the paper that these studies contribute nothing to the etiology of the disease. They do present a logical anatomic explanation for the persistent elevation of the blood pressure. There is one criticism that might be made of the work. How do the authors explain the low blood pressure in 4 of their patients with cerebral hemorrhage or softening? It is a well-known fact that individuals with a previously high blood pressure frequently have a cerebral catastrophe and that this event may be followed by a relatively low pressure.

# SURGERY

UNDER THE CHARGE OF

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**The Treatment of Peptic Ulcer from the Surgical Point of View.**—Woolsey (*Ann. Surg.*, 1926, **84**, 714) says duodenal and gastric ulcers should be studied separately. In duodenal ulcers medical treatment should be employed first with few exceptions. In series of cases treated medically the diagnosis is subject to error in perhaps 20 per cent and the majority of cases recur in time. Gastroenterostomy gives good results in about 90 per cent and its mortality as low as 2 per cent or less. A properly reduced acidity is essential to a cure of the ulcer, and this is accomplished in a large majority of cases by a properly performed gastroenterostomy, reaching to the most dependent part of the greater curvature. Gastroenterostomy prevents the recurrence of hemorrhage in about 87 per cent of cases. Jejunal ulcer should not occur in over 2 per cent if the acidity is properly reduced, if absorbable sutures are used, if foci of infection are removed and careful diet kept up for many months. These factors also form a good end result. Ulcers may recur in the stomach, duodenum or jejunum in 3 to 5 per cent. Such cases and some bleeding ulcers are suitable for resection. The reduction of acidity after resection is due to neutralization rather than to the removal of an acid-producing part of the stomach. Gastrectomy has a mortality two and a half times or more greater than that of gastroenterostomy and is not justifiable as a primary operation in all cases. Excision with gastroenterostomy or pyloroplasty is indicated in bleeding ulcers or small ulcers situated anteriorly. In gastric ulcers the danger of malignant degeneration demands the wide removal of the ulcer. The incidence of this degeneration is a matter of varying opinions, ranging from 2 to 30 per cent or even more. The presence of malignant invasion of an ulcer can only be determined clinically or excluded by gross examination at operation. Gastric ulcers are essentially surgical. There are several methods of operative removal of ulcers, excision by knife or cautery, Billroth I and II, mesogastric resection and Polya resection. The latter gives a low mortality and excellent results.

**Syphilitic Arthritis.**—Todd (*Brit. J. Surg.*, 1926, **14**, 260) states that syphilitic arthritis is not nearly as uncommon as it is commonly thought to be. There are many forms of syphilitic arthritis undoubtedly syphilitic that are not generally recognized, chiefly because the possibility is never entertained when the diagnosis is being made. Some

of them closely mimic other commoner conditions. No case of syphilis that has been efficiently treated ever develops syphilitic arthritis. The disease occurs in all stages of syphilis, both congenital and acquired. One should never diagnose rheumatism in any form until syphilis has been excluded as a possibility in the diagnosis. Likewise, the diagnosis of tuberculosis or any other form of arthritis must not be made until syphilis is excluded. Monarticular arthritis of a deforming type at any age, with or without pyrexia, may be syphilitic. Most important of all, a joint puncture with Wassermann reaction and cytologic examination of the fluid and a Wassermann reaction of the blood should be done as a routine in every case of arthritis of every kind. It may be taken as a clinical aphorism that acute rheumatism, which does not react to salicylates, is very apt to be syphilis. Clinical details may be stressed, particularly painlessness in spite of profuse hydrops, especially when this is associated with a perfectly free range of movement, symmetrical synovitis; general health is unimpaired in many cases in spite of prolonged joint affection.

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**The Newer Knowledge of the Biliary Function.**—SCHNEIDER (*Minn. Med.*, 1926, **9**, 631) claims that the most accurate and delicate single liver parenchyma function test in the absence of total duct obstruction is the play of urobilinogen in the fresh urine. In the presence of total duct obstruction and consequent jaundice the best functional test is the oral administration of bilirubin with the urinary consequences. In this latter situation if the parenchyma is normal no urobilin will appear in the urine. If it is damaged the degree of damage at the time of the test will be reflected proportionally in the urine. It goes without saying that hemolytic disease must naturally first be excluded.

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## PEDIATRICS

UNDER THE CHARGE OF

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**The Value of Elementary Phosphorus in Rickets.**—HESS and WEINSTOCK (*Am. J. Dis. Child.*, 1926, **32**, 483) found that the feeding of small amounts of elementary phosphorus to rats leads to the production of a phosphorus band at the epiphyses of the long bones. This consists of a transverse layer of dense, compact osseous tissue lying transversely immediately next to the proliferating cartilage. It is clearly seen on gross examination when the head of the bone is sectioned longitudinally and stands out prominently in the Roentgen ray picture. On microscopic examination, the band is found to consist of heavy trabeculæ of bone and to be limited to the subepiphyseal region of the shaft. As little as 0.007 mg. of phosphorus per day was enough to

bring about this change in the epiphysis. Elementary phosphorus, whether given in large or small doses was unable to prevent the occurrence of rickets in any degree whatsoever. Even when the diet was slightly rachitogenic the addition of phosphorus did not protect against rickets. Combining phosphorus with an inadequate amount of cod liver oil failed to render the oil a protection against rickets. These failures in protective action were noted on diets low in phosphorus as well as diets low in calcium. A marked increase in calcification of the long bones took place concurrently with the development of typical rachitic lesions. This indicates that rickets must be regarded not as the result of a failure of calcification, but as a disorder characterized by definite changes in the proliferative cartilage and in the growing bone. The demonstration of elementary phosphorus fails because it is unable to bring about calcification within this cartilage or to prevent the undue formation of osteoid tissue.

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**The Basal Metabolism and the Specific Dynamic Action of Foods in Children in Various Conditions of Nutrition.**—MORGAN and HATFIELD (*Am. J. Dis. Child.*, 1926, **32**, 516) studied the basal metabolism of 16 children from seven to fourteen years of age in varying states of nutrition. Ten of these patients were tested two or three times at an interval of a month or more. There was found an apparent lowering in metabolism in the spring as compared with the winter. The total heat production for twenty-four hours was compared to the standards of Benedict and Talbot. The 6 children classed as of normal weight according to the Baldwin-Wood standard showed metabolism falling within a 10 per cent ± deviation from standards by weight and by surface area. Two of the 4 girls classed as underweight showed nearly normal metabolism by all standards. The other 2 had high metabolic rates. Of the 6 children classed as overweight for height and age, 3 showed abnormally low metabolism, 2 had normal metabolisms and 1, which was possibly abnormal, gave 9 per cent above the standards. Ten out of 16 children exhibited basal metabolisms, therefore, within 10 per cent of the weight and surface standards of Benedict and Talbot, 3 of the 9 girls examined showed wider divergencies from the height standard of Benedict than from the older weight and surface-area standards; 4 boys, aged ten years, 2 distinctly overweight and 2 of normal weight, were tested for increase in metabolism following carbohydrate and protein meals. More than twice as much increase was noted after the protein meal as compared to the carbohydrate meal, but only small and irregular differences between the increases shown by the overweight and normal boys were obtained.

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**Fruit and Vegetable Juices Used in Infant Feeding.**—DAVIS and STILLMAN (*Am. J. Dis. Child.*, 1926, **32**, 524) conducted a series of experiments to determine the comparative growth-promoting qualities of several fruit and vegetable juices which have been recommended for child and infant feeding. Their results indicate that the tendency to substitute carrot, spinach or tomato juice for the conventional orange juice is justifiable. Winter cabbage did not seem to be as satisfactory for this purpose as the other vegetables studied. Their experiment did not show whether carrot or spinach juice was superior

to orange or tomato juice, as no attempts were made to determine the minimum amount of the juices which would support normal growth and nutrition in the rat. They observed, in their experiments, that the maturity of the vegetable and the length of time it has been stored appeared to affect its growth-promoting qualities. The winter cabbage, which contained very little juice, was rather poor in promoting growth, but fresh spring cabbage, which yielded more juice, supported growth better.

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**Peptic Digestion of Cows' Milk.**—Hess, Koch and Sennewald (*J. Am. Med. Assn.*, 1926, **87**, 1360) ran experiments *in vitro* to determine the effect of peptic digestion on fresh, raw, pasteurized and boiled milks, cultured lactic-acid milk and also on raw milk to which hydrochloric acid, lactic acid, phosphoric acid, lemon juice, orange juice, fresh and canned tomato juice, sodium citrate, sodium bicarbonate and lime water had been added. The results show that these various modifications affect the solubility of the milk proteins as well as the digestibility. The solubility of milk proteins was decreased by boiling and such increased acidity as occurred in these experiments. The solubility of milk proteins was increased by the introduction of weakly acid anions, by buffer salts and by autolysis. The digestion experiments *in vitro* indicate that aside from the physical character of the curd, there are several factors which influence peptic digestion of milk proteins. The most important of these aids to digestion are a lowered hydrogen-ion concentration and previous denaturization of the protein. Boiling milk definitely reduces its soluble protein content but facilitates digestion. The excellent results noted with cultured lactic-acid milk are in all probability due to the combination of small curd formation, a low hydrogen-ion concentration and the tendency to denaturization of its proteins. The total soluble nitrogen of orange-juice milk, made by the addition of 56 cc. of orange juice to the liter of milk, was even greater than that of cultured lactic-acid milk. This favorable action has been repeatedly demonstrated. Lemon-juice milk, made with 21 cc. of lemon juice per liter of milk, showed somewhat less digestion *in vitro* than other acid milks of a similar hydrogen-ion concentration. The results obtained when the modified milks were fed to young puppies showed that raw and pasteurized milks form large tough curds, while boiled and acidified milks form very small curds. As digestion progresses there is a tendency on the part of all curds to coalesce and to become firmer, although the boiled and acid-milk curds are soft and easily broken by pressure. Alkalinizing milk prevents any curd formation until the milk has been in the stomach longer than half an hour. At the end of two hours there is observed considerable curd formation and the curds are of large size. The determinations of the acidity of the gastric contents of puppies show that added acids lower the hydrogen-ion concentration only during the early stages of digestion. By the end of two hours the whey of the milk has largely disappeared from the stomach, carrying with it the added acids. The greatest value of all these milk modifications may lie in the soft broken curd which exposes a large surface to the digestion juice and to denaturization of the protein.

# DERMATOLOGY AND SYPHILIS

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**Failure of Early Abortive Treatment of Syphilis.**—Soon after exposure SUTTON's (*Arch. Dermatol. and Syph.*, 1926, **13**, 822) patient was given 0.45 gm. of neoarsphenamin intravenously, with instructions to return the next day for another injection, which she failed to do. Six weeks later she returned with an early maculopapular secondary eruption over her body, accompanied by general glandular enlargement and a few superficial mucous membrane erosions in the mouth. No primary lesion was demonstrated. Since the patient's husband had had a penile chancre swarming with spirochetes, and since exposure was denied subsequent to treatment, infection must have occurred prior to the injection. Thus it must be acknowledged that a single injection of neoarsphenamin is not always sufficient to abort infection with syphilis.

**Infantile Acne Vulgaris.**—The rarity of acne vulgaris in infants and its possible etiologic importance prompted AYRES (*Arch. Dermat. and Syph.*, 1926, **14**, 12) to report 3 cases occurring in apparently healthy boys, whose ages ranged from eight weeks to twenty-two months. Two of the patients were exclusively breast-fed when the eruption began. In a review of the literature during the past fifteen years only 1 case was found, reported by Beatty and Bigger in 1923. This occurrence in infants does not negate any endocrine contribution to the etiology of acne vulgaris, and emphasizes the importance of the changes occurring during puberty and adolescence in the causation of the disorder.

**Hair Dyes and their Toxic Effects.**—MCCAFFERTY (*Arch. Dermat. and Syph.*, 1926, **14**, 136) believes the vegetable hair dyes, such as henna, to be quite harmless unless used over long periods of time, when a brittleness of the hair tends to occur. Furthermore, the shades fade and the hair often takes on peculiar colors. All metallic dyes are dangerous; absorption is certain to take place sooner or later. Lead in the form of lead acetate has been for years the chief ingredient of many commercial hair dyes; silver in the form of silver nitrate has been the basis of several others. Compound hennas are dangerous because of the metallic substances which they contain; the amount of henna

is slight, and acts only as a carrier for the metal. The synthetic organic dyes are the most widely used preparations today. The most important member is paraphenylenediamin, which should not be used because of danger of consequent dermatitis. In fact, up to the present time there is no synthetic organic coloring for the hair which is entirely nontoxic. Bleaches, such as hydrogen peroxid, when freely used, may cause the hair to break. Dye removers are dangerous and should be prohibited from use in beauty shops.

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**Lymphogranulomatosis Inguinalis.**—Students and workers in tropical pathology for some twenty years have described a disease, the principal symptom of which was enlargement of the lymph nodes of the groin associated with fever, running an acute course. Because it was thought to be due to climatic influences, it has been termed "climatic bubo." PARDO-CASTELLO (*Arch. Dermat. and Syph.*, 1926, **14**, 35) has recently made an exhaustive study of a similar clinical condition in 3 patients, preferring the name "lymphogranulomatosis inguinalis," as proposed by Nicholas, Durand and Favré. He believes this condition to be an infectious and contagious disorder transmitted by sexual intercourse. The initial lesion appears on the genitals, and while it may be papular, erosive or herpes-like, it is nearly always single, small, slightly inflammatory, nonindurated, clean and painless, and discharges a small amount of serous fluid. It heals quickly without treatment and disappears in a few days, leaving no trace. Hence one seldom seels the primary lesion; the author observed one of the erosive type in his cases. The incubation period is three weeks in most cases. Extragenital lesions are rare. The painful inguinal adenitis appears in about two weeks. The adenopathy is discrete, hard, painful and soon becomes fixed. It is usually unilateral, and in practically every case the glands are involved to the region above and behind Poupart's ligament. The lymphatic inflammatory mass runs its course in from one to several months, it being liberated by a sudden rupture of the overlying edematous skin, draining through a sinus until completely involuted. The sinuses heal, leaving thick, puckered, retracted scars. The usual constitutional symptoms of fever prevail during the stage of adenopathy; the temperature may be high enough to induce delirium. In all cases reported (including the author's) no microörganisms have been discovered, neither in the initial lesion nor in the glands. Blood cultures have been negative and the blood findings are usually normal, save an occasional leukocytosis. As to the pathology in the glands the author found the picture of an infectious granuloma with abscess formation of the miliary type—2 yielding quite promptly to surgical intervention (1 patient disappeared before treatment had been initiated). Surgical interference is the treatment of choice, especially after sinus formation, although other observers have produced good results with Lugol's solution intravenously. Most investigators believe climatic bubo and lymphogranulomatosis inguinalis to be identical clinical entities; the etiology remains unknown.

# OBSTETRICS

UNDER THE CHARGE OF

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**Pregnancy Complicating Exophthalmic Goiter.**—MUSSEY, PLUMMER and BOOTHBY (*J. Am. Med. Assn.*, 1926, **87**, 1009) have made quite clear a subject which is often misunderstood and misleading if the literature of this complication be followed closely. They classify the different types of goiter and confine this article only to the hyperfunctioning adenomatous goiter and exophthalmic goiter. They lay decided stress and warning on the use of iodin, given as a therapeutic agent to patients who have adenomatous goiter without hyperthyroidism, and to patients over twenty-five years of age who have diffuse colloid goiter. This warning is particularly pertinent in cases of pregnancy. They describe exophthalmic goiter as a constitutional disease and characterize it by a parenchymatous change in the gland, a high basal metabolic rate with a peculiar nervous syndrome and a tendency toward the gastrointestinal crises of vomiting and diarrhea. They further take up the work of Sandiford and Wheeler relative to the metabolic rate in the course of normal pregnancy and particularly call attention to the rapid increase that occurs in the last three months of pregnancy, and give as their reasons for the increase, not the presence of an excess of thyroxin in the tissues of the mother, but that the elevation is caused by an increase in the amount of protoplasmic tissue, due largely to the growing fetus. In the early months of pregnancy the metabolic rate is not increased materially as a result of the pregnancy, but at the end of the approach of term this rate may be 20 to 25 per cent above the Du Bois standard. In only a very small percentage, about 2 out of 32 cases, could the onset of exophthalmic goiter be considered with reasonable certainty to have developed during the pregnancy, and when so occurring, the onset was rapid and sever and characteristic of the crises stage of toxic goiter. All but 2 women of this series became pregnant during the course of exophthalmic goiter, several after ligation of the superior thyroid arteries and several more following partial thyroidectomy. The largest percentage of pregnant cases with exophthalmic goiter were delivered at term, while others aborted, a few miscarried, a few were delivered prematurely. The methods of treatment used for the relief of exophthalmic goiter in pregnancy were divided into two groups. The therapeutic and operative treatment. The operative consisted of ligation or partial thyroidectomy, the compound solution of iodin (Lugol solution)

was the therapeutic agent used. The conclusions drawn were that both the course of pregnancy and the maternal and fetal mortality were not appreciably affected as the result of the syndrome present if proper therapeutic and operative measures advised were carried out.

**Recurrent Toxemia of Pregnancy.**—Von Geldern (*California and West. Med.*, 1926, **25**, 333) discusses the question of whether a severe toxemia occurring in one pregnancy would necessarily recur in future pregnancies. There is a variance of results, but the concensus of opinion is that from 18 to 21 per cent of cases who suffered grave toxemias in one pregnancy showed recurrence in subsequent pregnancies. The chronic nephritis patients are separated from this group. The earlier the reduction of albumin to a faint trace and the prompt return of the blood pressure to normal, the more favorable the prognosis. In those cases whose hypertension and renal lesions were present eight weeks post partum a more grave prognosis is indicated. In one series of eclampsia cases 11 per cent who returned for study showed evidence of chronic nephritis. It has been clearly shown that in patients who suffered from preëclamptic toxemia and eclampsia that many of these show no evidence in careful clinical study until a pregnancy interferes and that a patient who has once suffered severe kidney lesion and come under care for another pregnancy will, in all probability, undergo a recurrence.

## GYNECOLOGY

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**Cancer and Diet.**—In discussing the relationship of diet to the occurrence of cancer, Charles (*J. Cancer*, 1926, **3**, 1), who is medical superintendent of the City of Dublin Cancer Hospital, states that a healthy body functioning efficiently can resist disease and the healthy body is almost entirely a matter of proper feeding. It is to food, therefore, that the greatest attention must be given. The adulteration of food and the use of preservatives should be forbidden as a matter of common sense, and beyond that some method of intruction in feeding and food values must be devised for the guidance of the public. Individuals should avoid "doped" food of all kinds, and eat fresh natural food, pure whole milk and butter, fresh eggs, cheese, salads, raw fruits, vegetables, not overcooked or cooked with soda, whole-meal bread, brown sugar, black treacle, all of which are rich in vitamins. The skins and rinds of fruits and vegetables, usually thrown away, are very valuable. Outdoor exercise, more frequent evacuations, and, if necessary, the use of liquid paraffin daily as a purgative, are all defensives against cancer. The prevention of cancer is of the

utmost importance and no cure has yet proved effective. Therefore, proper feeding must be inculcated, the use of outdoor exercise, the avoidance of constipation and of overheated foods must be taught.

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**New Operation for Tubal Implantation.**—Although in this country most gynecologists have ceased to have much confidence in any operative procedure for the reëstablishment of a tubal lumen which has once been closed there is quite a bit of experimentation in this field of surgery in Europe. In a communication from KIPARSKY (*Zentralbl. f. Gynäk.*, 1926, **50**, 1523), of Leningrad, he states that the objection to the usual technique of implantation of the tube into the uterus is that the linear scar which results is very apt to close off the opening of the tube as it later contracts. To overcome this objection he has modified the technique by the introduction of a special instrument which is shaped like a sharp cannula and by means of which he makes a round opening in the uterine cornu, into which the tube can be implanted. In performing the operation the uterus is drawn into the wound and the cannula is forced through the cornu following the direction of the interstitial portion of the tube as closely as possible. While the cannula is in this position a catgut ligature is inserted through both uterine walls passing through openings in the end of the cannula so that when the cannula is withdrawn a loop of the ligature is pulled out with it. The loop is then cut in the middle and each end of the cut portion is passed through one lip of the split uterine end of the tube. By pulling on the free ends of the ligature the tube is then drawn into the cornu of the uterus through the previously prepared opening and sutured in place. The author claims that the technique is very simple and should give better results than the operations which have been previously performed for this purpose.

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**Iodized Oil in Pyelography.**—Recently iodized oil has been used in many regions of the body to render nonopaque organs visible by means of the Roentgen ray. NEUSWANGER (*Surg., Gynec. and Obst.*, 1926, **43**, 169) has been experimenting with the use of this substance as a pyelographic medium. As the result of his experiences, he concludes that iodized oil, 40 per cent, has no marked bactericidal or bacteriostatic properties. Iodized oil, 40 per cent, injected intravenously in dogs in quantities three times that used for the average pyelogram and ureterogram may produce areas of congestion and hemorrhage in the lungs without any permanent anatomic change, the animals showing no symptoms of irritation or toxicity over a period of two months. It may be used to inject the urinary tract in laboratory animals and patients without resulting symptoms of irritation or toxicity. This preparation appears to offer a pyelographic medium which is superior to those in use at the present time in regard to toxicity and degree of opacity to the Roentgen ray. It was found to be especially useful in obese patients and even a small injection of 1 to 2 cc. into the ureter gave a very dense shadow. Ureteral injections were found to be more complete with iodized oil than sodium iodide in several instances in which a direct comparison was made. The oil was found to escape readily from the urinary tract and Roentgen ray examinations twelve hours following the injection gave no evidence of residual oil within the renal pelvis or ureter.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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**The Function of the Tonsils.**—After massaging the tonsils of 18 healthy individuals, SCHMIDT (*Ugesk. f. Læger*, 1926, **88**, 613) noted a decrease in the leukocyte count, particularly in the lymphocytes. The author interpreted this finding as indicating that an antibody was forced into the peripheral blood stream which produced the leukopenia. On the other hand, massage of actively inflamed tonsils produce a polymorphonuclear leukocytosis.

**Hematologic Investigations of Some Infections in the Throat and in Children with Adenoid Growths.**—SCHMIDT (*Ann. Otol., Rhinol., and Laryngol.*, 1926, **35**, 249), with the idea of ascertaining "whether the difference in the blood picture of scarlatinous angina and ordinary angina is also present in mild cases of scarlatinous angina, where the diagnosis cannot be made until after a shorter or longer time of observation, to the end that the diagnosis of scarlatinous angina may possibly be supported or rejected by hematologic examination," gives a very comprehensive dissertation on the history, technique and the results of his investigations on the leukocytic incidence in normal adults and children, as well as those affected with various diseases of the nasopharynx. By using the separated pipettes and mixing glasses devised by Ellermann and Erlandsen and by pipetting off a constant quantity of the fluid for each count in a Fuchs-Rosenthal's counting chamber, the mean error was found to increase from 4.96 per cent in the average of 129 to 10.45 per cent in an average of 47. In 22 normal adults the highest number of leukocytes was 10,200, the lowest 6100 and the average 7959. In normal children there was a gradual decrease of lymphocytes up to the age of eight years, with a corresponding increase in the total leukocyte count. The eosinophil cells diminished in number throughout childhood, while the number of monocytes remained quite constant. Children with adenoid growths showed a lower lymphocytic count than normal children, whereas the total leukocytic polymorphonuclear neutrophilic and eosinophilic counts tended to be higher. In 63 cases of mild scarlatina, 49 had, during the first two or three weeks after admission to the hospital, a somewhat varying leukocytosis, in every patient being at least once above the range of error, that is, above 12,000, while 11 patients had counts between 10,000 and 12,000. Of 36 cases of undoubted scarlatina, all but 2 showed a leukocyte count varying from 10,000 to 19,000 and 22 gave an eosinophilic content of the blood between 5 and 10.5 per cent. Fifty-eight persons without scarlatina did not yield a leukocytosis in the nonfebrile stage, while 28 of the same category showed a leukocy-

tosis which could be explained clinically. Individuals with peritonsillar phlegmon and abscess showed a leukocytosis ranging from 15,000 to 30,000. The total leukocyte count fell rapidly and decisively when the abscesses were incised, whereas no fall was noted after incision of peritonsillar phlegmon. Tonsillar abscess frequently gave rise to a leukocytosis of from 13,000 to 20,000, often in the absence of increased temperature. In patients with chronic tonsillitis pus was often found in the tonsils, but the leukocytic count was normal. In the acute stages of tonsillitis, however, there was a leukocytosis, even without fever. Persons with simple tonsillar hyperplasia and chronic pharyngitis had no leukocytosis. The author believes that in tonsillar abscess the existence of a leukocytosis in connection with the subjective complaints affords a more reliable indication of the infectious state of the patient than the relations of the temperature and the pulse.

## RADIOLOGY

UNDER THE CHARGE OF

ASSISTED BY

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**The Roentgenologic Findings in Ulcerative Colitis.**—CARMAN and MOORE (*Am. J. Roentgenol. and Rad. Therapy*, 1926, **16**, 17) define ulcerative colitis as that form of colonic ulceration not caused by infestation with parasites, tuberculosis, dysentery, actinomycosis, or syphilis. The disease is by no means uncommon. Logan collected records of about 600 cases seen at the Mayo Clinic, and clinical and necropsy records contain many references to the disease. Logan describes two distinct clinical types, in both of which profuse diarrhea is the chief complaint. In 1 of these the condition is more or less chronic, and the patients show but little systemic reaction; in the other the condition is acute and is accompanied by extreme prostration. With the proctoscope, areas of ulceration which begin in the rectum and extend upward are characteristic and are easily recognized. The roentgenologic findings are explained by an understanding of the pathologic changes found in the wall of the large bowel. The process begins in the rectum as multiple small superficial ulcers, which in the early stages involve only the mucosa. These ulcers alternately heal and break down, gradually extending upward until the entire large bowel is involved. The process rarely, if ever, extends beyond the ileocecal valve. The stage of superficial ulceration is followed by a deeper penetration of the intestinal coats, with round-cell infiltration, abscess formation and resulting fibrosis which greatly thickens the wall of the bowel and reduces the size of its lumen. In their experience

examination by the barium enema is more satisfactory. Evidences of spasm, irregularities or encroachments on the lumen of the bowel are suggestive. Rapid filling of the entire large bowel, marked narrowing of the lumen and absence of haustration, with areas of contraction giving the "string-of-sausage" appearance are pathognomonic. Points of differentiation from carcinoma, syphilis, tuberculosis, diverticulitis and diverticulosis and actinomycosis are given. Amœba histolytica and other parasites in their experience produce no abnormal roentgenologic findings. Certain types of chronic constipation, accompanied by extreme atony of the large bowel show dilatation and flexibility where ulcerative colitis shows contraction and rigidity. The roentgenologic examination furnishes but one link in the chain of evidence and must be used in collaboration with the clinical and proctoscopic findings.

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**Osteochondritis or Epiphysitis.** — CHRISTIE (*J. Am. Med. Assn.*, 1926, **87**, 291) briefly considers the anatomy of the epiphyses, and considers the pathologic condition that has been variously named osteochondritis, epiphysitis and osteochondropathy, and which in special regions of the body has been given many descriptive designations or has been named after its discoverers or discoverer. The epiphyses at birth are composed of cartilage, with the exception of those of the lower end of the femur and the upper end of the tibia, which are partly ossified. Increase in bone length takes place at the epiphyses. In the long bones ossification always proceeds more rapidly at one end than at the other, and is more rapid and continues longer at the end of the epiphysis last united to the shaft. Although in maturity the epiphyses freely communicate with the diaphysis, in earlier life the epiphyses are completely shut off from the diaphysis by the epiphyseal cartilage. It is only in disease conditions, especially in rickets, that the cartilaginous line is penetrated by the bloodvessels. Ossification takes place from the center of the epiphysis and proceeds toward the periphery until the entire epiphysis is ossified, with the exception of a thin layer at the junction of the shaft forming the epiphyseal cartilage or disk. There seems little doubt that the etiologic factors and the pathologic changes are similar in Legg's disease, Schlatter's disease, Kohler's disease, of the tarsal scaphoid and Kohler's disease of the head of the second metatarsus. Recently another condition, vertebral epiphysitis, has been added to the list, and it is quite probable that the same disease occurs in other epiphyses, especially those subject to trauma, such as those of the os calcis and olecranon. There is also fairly good evidence that the osteochondritis dessicans of Konig and the rare condition called malacia of the semilunar bone belong to the same category. There is no general agreement on the etiology or epiphysitis except that it is quite definitely known that the disease is not tuberculous, rachitic or syphilitic. The infectious theory has little to support it, and that of the endocrine origin is a pure assumption with no reliable evidence to support it. The conditions occur in locations that are subject to long-continued trauma, such as weight bearing, pressure or muscular pull, and it is interesting to note that each lesion is associated with a definite age period, and that in each the age period is that in which the affected bone nucleus normally is actively developing.

# NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**Lemniscus Symptoms following Epidemic Encephalitis: Bilateral Impairment of Deep Sensation.**—CADWALADER (*Arch. Neurol. and Psychiat.*, 1926, **16**, 605) reported 3 cases, believed by him to be cases of epidemic encephalitis, in which the onset of symptoms following in the wake of an attack of "flu" were characterized by remissions and exacerbations and associated with ocular paralysis. In each case there was abrupt bilateral impairment of deep sensation, probably due to a lesion in the medulla oblongata implicating the lemniscus. The motor symptoms in these cases were probably the result of involvement of the pyramidal tracts anterior but adjacent to the lemniscus.

**Intracranial Pressure Changes during Forced Drainage of the Central Nervous System.**—Following experiments on dogs, KUBIE (*Arch. Neurol. and Psychiat.*, 1926, **16**, 319) believes that the intravenous injection of isotonic or hypotonic solutions does not materially increase the intracranial pressure when cerebrospinal fluid is allowed to escape during the course of the experiment. The possible influence of this procedure on certain types of central nervous system infections is to be further investigated.

**The Significance of Gain in Weight in the Malaria Treatment of General Paralysis.**—In a study of 62 cases of general paralysis treated with malaria, BUNKER (*Arch. Neurol. and Psychiat.*, 1926, **16**, 329) found 80 per cent showed an increase of 10.3 per cent of their pretreatment weight during the first three months following the termination of the malaria. This increase in weight occurred in 95 per cent of patient attaining full remissions. The maximum gain in weight was obtained in the first six months, following which there was a tendency to a slight decline, due largely to the "unimproved" cases. Failure to recover part or all of the weight lost during the course of malaria seemed to be of unfavorable prognostic significance. Conversely, gain in weight following treatment was frequently, to a certain extent, coincident with mental improvement, although improvement was in some cases only temporary. The post-treatment gain in weight is probably connected more or less intimately with the mechanism of the malaria therapy, and is suggestive of a fundamental alteration in the vital processes of the organism, which in some obscure way underlies the striking therapeutic results following malaria treatment.

**A Study of Delirium.**—ZIEGLER (*Am. J. Psychiat.*, 1926, **6**, 105), in a study of data obtained from 375 individuals comprising several groups, found that typhoid fever, pneumonia and influenza were

most commonly associated with the deliriums studied, although in each case the type of the delirium was determined by the personality of the individual. The chief characteristics of the deliriums studied were: "Push of irrational talk, vocal and general motor restlessness, visual hallucinations (rather than auditory) of moving objects, animals or people, peculiar feelings, unreality feelings, delusions that are transitory and annoying, blind groping, sleepiness, defective perception and distorted awareness of environment." Delirium, while occurring slightly oftener in psychopathic patients than in normal individuals, occurred less frequently in individuals who had lived for thirty-one years at an altitude of 10,200 feet than in those living at sea level. The author believes that delirium is probably a distinct entity.

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**A Study of Psychoses Occurring in Relations to Childbirth.**—KILPATRICK and TIEBOUT (*Am. J. Psychiat.*, 1926, **6**, 144) found that they were not peculiar to childbirth and were essentially the same as psychoses occurring at other times. Of the 72 cases studied, 32 per cent were deliria, 50 per cent manic-depressive psychoses, 14 per cent dementia precox and 4 per cent psychoneuroses. Over half of the deliria were apparently nontoxic and three-fourths of the manic-depressive group were depressed in which the element of confusion was more constant in those with an accompanying physical factor. All of the dementia precox group were paranoid in reaction and none of these have recovered after five years.

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**Roentgenologic Exploration of the Central Nervous System with Iodized Oil (Lipiodol).**—SICARD-FORESTIER (*Arch. Neurol. and Psychiat.*, 1926, **16**, 420) claims that lipiodol may be used in several ways for exploration and diagnosis of conditions of the central nervous system. In destructive affections of the spine the epidural injection of 3 to 6 cc. aids in the making of a correct diagnosis. Lipiodol injected into the subarachnoid space, either cisternally or by the lumbar route, furnishes a means of accurately demonstrating compression or obstruction of the spinal canal or cord, and demarcating its limits. In one-third of the cases in which lipiodol was thus used localization and diagnosis was made before the appearance of any objective disturbances in sensibility. A further advantage of this method is that localization is made in reference to the spine rather than to the segment. Light lipiodol (ordinary lipiodol diluted with olive oil) in which the specific gravity is less than that of the spinal fluid may be used to outline the ventricles especially if made into an emulsion with spinal fluid before injection.

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**A Sign and Symptom of Spinal-cord Tumors.**—In the study of a recent case of tumor of the spinal cord DANDY (*Arch. Neurol. and Psychiat.*, 1926, **16**, 435) found that the characteristic symptoms of this condition repeatedly and suddenly developed following straining at stool. He believes that anything which increases the intraspinous pressure, such as sneezing, coughing and straining at stool, tends to force the spinal cord downward against the tumor. The resulting trauma manifests itself in motor, sensory and sphincteric disturbances and backache noted in tumors of the spinal cord. The sudden onset of the symptoms following straining may be of importance in the differential diagnosis of cord tumors.

# PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**Cases of Periarteritis Associated with Polyneuritis.**—The literature showed about 10 cases of this nature previous to BALO's (*Virchow's Arch. f. path. Anat.*, 1926, **259**, 773) account of 3 in human beings and 1 in a dog, all of which came under his attention within the space of eight months. Although no relationship between these cases could be traced, their rapid occurrence raised the possibility of an infective origin. In each of the 3 cases fever was present and an exanthematous eruption appeared. The course of the disease was three, four and six months respectively. Pain and lameness characterized the cases and in 2 pressure over the superficial nerve trunks was very painful. The necropsy findings were peculiar in revealing nodules on the arteries, with localizations which varied in the different cases. In the case showing muscle atrophies the bloodvessels in the muscles showed nodules and the author regards this as evidence in support of the claim that the vessel and not the nerve changes were primary. The presence of infarcts was noted mainly in the liver, spleen and kidneys, and the infiltrative cells were leukocytic rather than lymphocytic in type. The etiologic factors which had been suggested were briefly mechanical, toxic, congenital defect, infectious and luetic. The last view is untenable in view of the occurrence of periarteritis nodosa in animals, which are not susceptible to syphilis, also in that all 3 cases here reported gave negative Wassermanns at the time of the disease. Then, too, the arterial changes were first noted in the adventitia. Animal inoculations seemed to disprove any relationship between streptococcus and the disease, but injections of pulverized nodules gave evidence that the disease was a new malady caused by a filterable virus, with an affinity for the bloodvessels. The acute infective nature of the condition is upheld by the febrile, eruptive symptoms, leukocytic infiltration, as well as enlargement of the spleen and lymph nodes.

**Extraordinary Giant-cell Formation in Acute Myeloblastic Leukemia.**—The case reported by KOERNER (*Virchow's Arch. f. path. Anat.*, 1926, **259**, 617) was that of a male, aged sixty-eight years, who showed no physical signs to lead to the above diagnosis except a few petechiæ and an enlarged splenic dullness. The blood showed hemoglobin, about 20 per cent; erythrocytes, 1,200,000; there was a slight leukocytosis with a large predominance of immature cells of the order of myelocytes and myeloblasts. Marked changes were noted in the liver, spleen

and lymph nodes, the liver and spleen being greatly enlarged; also the bone marrow was of a dirty gray color. On histologic investigation, the liver, spleen and lymph nodes and, to a less degree, the lungs, heart and other organs showed many giant cells grouped in the interstitium and surrounded by a "myeloid reaction." There was associated a marked proliferation of the reticuloendothelial cells which seemed aggregated about the capillaries. The point of interest is the greater prevalence of the giant cells in the hemopoietic organs. The origin of of these cells was suggested by Aschoff in reviewing 93 cases of various acute infections as of: (1) Local origin arising from endothelium; (2) excessive growth of the white cells; (3) infiltration from surrounding tissue; (4) emboli from the bone marrow. Aschoff favored this last view. The author and Barth found no giant cells in the blood stream and few in the bone marrow and so the fourth origin seems unlikely, especially as these two authorities claim that the homogeneous protoplasm of the giant cell is markedly divergent from the megakaryocyte. On the other hand, their histologic studies support the theory of a transition from endothelial cells to giant cells. The etiology of this condition was not established, but it would seem to be some poison acting particularly upon the hemopoietic organs, stimulating myeloid response and endothelial proliferation leading to giant-cell formation.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Rocky Mountain Spotted Fever.**—PARKER and SPENCER (*Pub. Health Repts.*, 1926, **41**, 461) give the following discussion and summary of their work: The data as presented show the following: (1) That, although of known infected adult ticks the majority of those containing rickettsia were infective, yet of each lot tested a small group of noninfective ticks contained rickettsia morphologically identical, while still another small group was infectious though the tick smears were entirely free of organisms. (2) That of wild ticks from a known infected area a considerable proportion contained rickettsia indistinguishable from those associated with spotted fever, and that the smear and inoculation results of such ticks were parallel with those of the known infected group. (3) That a small proportion of wild ticks from a supposedly uninfected area contained similar rickettsia, but

none caused infection. It is difficult to account for the noninfective rickettsia which were present in part of the known infected, laboratory-reared ticks, and which exhibited a morphology identical with that of the rickettsia in fever-producing ticks of the same group. They may represent an avirulent phase of the spotted fever virus, although the nonpathogenic nature of these bodies cannot, of course, be ruled out. This accords with previous observations of tick virus in a similar lot of known infected ticks by which we demonstrated various degrees of virulence for guinea pigs ranging from a noninfective or an immunizing phase in *unfed*, æstivating or hibernating, ticks to an active highly virulent phase *following feeding*. The term "reactivation" has been used to designate this transition, which has been repeatedly observed in known infected lots. For example, in recently infected larvæ the virus is present but is noninfective unless massive doses are used (5 engorged larvæ very rarely infect; 25 usually, but not always cause infection, often of a mild character); in the resultant *unfed* hibernating nymphs the virus is present either in a noninfective or immunizing phase, but in the *fed* nymphs it has acquired marked virulence; a noninfectious or immunizing phase is again encountered in the resultant *unfed*, æstivating, or hibernating, adults, but in *fed* adults a high degree of virulence has been reacquired. In presenting these observations we realize that the relatively small part of the tissue of a tick represented by our smear preparations cannot be taken as absolute evidence of the absence of rickettsia from the entire tick. However, it is at least reasonable to believe that they were few in number, since the test ticks had all ingested blood and the rickettsia had thus been afforded, as we have shown, the most favorable conditions for multiplication and distribution throughout the various tissues. There is, of course, the possibility that they were present in an unrecognized form.

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**Hemolytic Streptococci of the Beta Type in Certified Milk.**—Brown, Frost and Shaw (*J. Infect. Dis.*, 1926, **38**, 381) found β-hemolytic streptococci in considerable numbers in the certified milk of five dairy herds. These streptococci belonged to several distinct cultural and serologic groups. There is no evidence that any of them, whether from gargety cows or from mixed milk, are pathogenic for human beings. The causative organism of milk-borne septic sore throat is Streptococcus epidemicus. This streptococcus is probably of human origin but occasionally may gain entrance to the udder of a cow and find its way into the milk supply. The hemolytic streptococci commonly found in milk show distinct cultural and biologic differences from Streptococcus epidemicus. No single test, however, can be relied upon to differentiate them. All of the tests listed are of value. A few bovine strains may possess capsules. Many produce rapid hemolysis of blood cells in fluid media. A considerable number are markedly pathogenic for mice. Many ferment the same sugars as the human strains. A few produce about the same final hydrogen-ion concentration in glucose broth as do the human strains, and a few resemble the latter in producing little or no hydrolysis of sodium hippurate. The latter two tests, however, are probably the most constant and reliable of those tried. To justify condemnation of the milk the streptococcus found should correspond in all respects with the characters of Streptococcus epidemicus as listed.

# PHYSIOLOGY

PROCEEDINGS OF

## THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 15, 1926.

**The Inorganic Constituents of the Blood after the Injection of Parathyroid Extract.**—D. W. WILSON and C. RIEGEL (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). Studies on the parathyroid glands are of interest on account of the remarkable changes induced in the body as a result of their removal. A day or two after parathyroidectomy tetany develops and death quickly ensues. The outstanding change which has been found in the chemical composition of the blood is a lowered calcium concentration. Recently Collip has prepared an extract of the parathyroids which will not only relieve the tetany of parathyroidectomized animals, but will raise the blood calcium. In normal animals repeated injections of the extract cause the calcium of the blood to rise as much as twice its normal concentration. Accompanying the high blood calcium there is an increase in the inorganic phosphate of the serum and a decrease in serum chlorid. Such changes in the inorganic constituents of the blood have suggested that the concentration of other inorganic substances might also be altered. We have therefore analyzed the blood corpuscles and serum of dogs after repeated injections of parathyroid extract for water, calcium, inorganic phosphates, sodium, potassium and chlorid. We have observed the rise in calcium and and phosphate and the fall in chlorid of the serum. Accompanying this there is a fall of sodium and a delayed rise of potassium. In the corpuscles the sodium diminishes and potassium rises parallel with the changes in the serum. There is little change in the water of either serum or corpuscles. These results demonstrate that there is an unusually large loss of sodium chlorid from the blood without a corresponding loss of water. The observation that there are parallel changes in sodium and potassium in serum and cells is of considerable importance because it indicates that the cell membrane is permeable to these two ions. This contradicts the opinion prevailing at present. These experiments support and extend the knowledge concerning the regulation of the concentrations of the inorganic constituents in the blood by the parathyroid glands.

**The First Dissociation Constant of Carbonic Acid in Red Blood Cells.**—W. C. STADIE and E. C. ROSS (from the John Herr Musser Department of Research Medicine, University of Pennsylvania). The first part of the paper discusses the theoretical and experimental factors involved in determining by means of the hydrogen electrode the hydrogen-ion concentration of a solution containing hemoglobin, sodium bicarbonate and sodium chlorid. Wherever possible the factors were

tested experimentally and it was found that while absolute values may be inexact perhaps to the extent of 0.05 to 0.1 pH units, comparative values at a single temperature are valid up to the experimental limits of the method, *i. e.*, about ±0.01 pH units. It was further found that not only does the hydrogen electrode give true pH values (within the limitations noted above) in a simple solution of $NaHCO_3$, $H_2CO_3$ and NaCl, but also in the presence of a high hemoglobin concentration (*i. e.*, 20 mM = the concentration within the red cell). The derivatives of hemoglobin, viz: reduced hemoglobin, carbon-monoxid hemoglobin, nitric-oxid hemoglobin, methemoglobin and cyan hemoglobin also do not interfere with pH determinations.

The second part of the paper is an attempt to calculate the pH of the inside of the red blood cell by determining the first dissociation constant, $pK_1'$ of carbonic acid. The Henderson-Hasselbalch equation:

$$pH = pK_1' + \log \frac{NaHCO_3}{H_2CO_3}$$

allows this calculation if pH, $NaHCO_3$ and $H_2CO_3$ are known. Reduced and carbon-monoxid hemoglobin were equilibrated at known $CO_2$ tensions pH, $NaHCO_3$ and $H_2CO_3$ determined and $pK_1'$ calculated. It was found that in solutions in which the hemoglobin varied from 2.5 mM to 20 mM and NaCl + $NaHCO_3$ from 40 mM to 500 mM, $pK_1$ followed closely a law known as the Debye-Huckel law, viz.:

$$pK_1' = pK_1 - \beta\sqrt{\mu}$$

$pK_1$ is a constant = the first disocciation constant at infinite dilution, *i. e.*, in the complete absence of salts. This value is obtained by extrapolation from the known values at finite salt concentrations.

$\beta$ depends upon the concentration of hemoglobin and its state, *i. e.*, whether reduced or oxidized.

$\mu$ equals the total concentration of electrolytes (univalent) present.

For hemoglobin concentration of 20 mM and $\mu$ = 120, which is the condition in the interior of the red cell, it was found that $pK_1'$ is different for reduced hemoglobin and carbon-monoxid hemoglobin and presumably oxyhemoglobin, *i. e.*, $pK^1$ for reduced hemoglobin in cells is 5.90, $pK^{1\prime}$ for oxyhemoglobin in cells is 6.00, whereas $pK_1'$ in the absence of hemoglobin is 6.12. This means that if the cell loses oxygen it becomes more acid and *vice versa*. The exact physiologic significance of this mechanism is not known, but it is suggested that it may possibly be a mechanism to keep the $CO_2$ pressure constant within the blood.

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**The Accessibility of the Glomeruli of the Frog's Kidney to Renal Portal Perfusion.**—A. N. RICHARDS and A. M. WALKER (from the Laboratory of Pharmacology, University of Pennsylvania School of Medicine). A belief in the secretory activity of the renal tubules receives a measure of support from certain experiments on the frog. Such experiments have taken advantage of the double blood supply of the frog's kidney; they have been largely perfusion in method; it is their common evidence that certain of the urinary constituents can be

secreted by the tubule epithelium. The validity of the evidence so secured depends upon the supposed ability to isolate completely the tubular from the glomerular circulation; to confine, that is, the renal portal perfusion fluid to the tubular capillaries and not permit it access to the glomeruli.

Bainbridge, Collins and Menzies pointed out some years ago that fluid perfused through the renal portal vein under a pressure of 40 cm. of water did, in fact, reach the glomeruli. By the addition of india ink and of ferric ammonium citrate to the venous perfusion fluid, we have been able to show that a venous perfusion of 10 cm. pressure followed a similar course (45 to 89 per cent of the glomeruli being involved); that this distribution is not substantially altered by the presence of a simultaneous aortic perfusion under a pressure two to four times that existant in the venous system; that even venous perfusions of a far lower order of pressure (2 to 4 cm.) reach a considerable number of glomeruli. In explanation of this extreme accessibility of the glomeruli to venous perfusion fluid, we offer evidence that during double perfusion many glomeruli are more patent to perfusion from the venous than from the arterial side, regardless of the pressure employed.

We conclude that it is impossible to entirely confine renal portal perfusion fluid to the tubular capillaries; that experiments which base their evidence of tubular secretion on the ability to affect such a distribution cannot be regarded as unequivocal.

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**The Osmotic Pressure of Hemoglobin as Influenced by Salt Concentration.**—J. H. AUSTIN and F. W. SUNDERMAN (from the John Herr Musser Department of Research Medicine, University of Pennsylvania).

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